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ENZYMATIC SYNTHESIS OF KOJIC ACID ESTERS AND ANALYSIS OF DEPIGMENTING ACTIVITIES USING IN VITRO AND IN VIVO MODELS

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By

AHMAD FIRDAUS BIN LAJIS

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Kojic acid (KA) is a commonly known skin-whitening agent in cosmetic products. However, KA is not oil soluble that makes it difficult to be incorporated in cosmetic formulation. Therefore, KA esters are synthesized to increase its lipophilicity that allows it to be easily incorporated into cosmetic products. In previous study, kojic acid esters were synthesized via chemical processes using chemical catalysts. Chemical catalysts are not environmentally friendly and caused more harm to consumers compared to biocatalyst. The handling process and removal of hazardous chemical from products may also increase cost of production. In this study, the enzymatic synthesis of KA esters was proposed and performed in various types of bioreactor such as stirred tank reactor (STR), packed bed reactor (PBR) and fluidized reactor (FR) using three commercial immobilized lipases (TLIM, RMIM and N435) where the performances were compared. The alternative approaches and methods (solvent and solvent-free systems) for the synthesis of KA esters in different reactor systems were also investigated. Various enzymatic and bioreactor operation parameters were manipulated aimed at solving various problems in enzymatic reactor operation such as shear effects due to stirring and potential of lipase reusability. The physical, chemical and depigmenting properties of KA esters were also studied. The depigmenting activity of KA esters was evaluated using *in vitro* and *in vivo* models using B16F1 and zebrafish embryo, respectively.

For esterification using N435 lipase, very high yield (up to 50%) of KA esters were synthesized in STR compared to PBR and FR. The enzymatic esterification of KA esters in STR would currently be the best alternative as compared to other types of reactor tested, despite some of its weaknesses. Solvent-free system can be another alternative but the handling of saturated fatty acid in liquid form can be difficult because high temperature is required. Under ultraviolet (UV) light, skin color turn dark due to an increase of alpha-melanocyte stimulating hormone (α-MSH) and oxidation process. Kojic acid monopalmitate (KAMP) showed slightly higher inhibition to melanin formation compared to KA, kojic acid

monooleate (KAMO) and kojic acid monolaurate (KAML), as analysed by *in vitro* model using α-MSH stimulated B16F1 cells. The reduction of melanin formation was correlated to the reduction of mushroom tyrosinase and cellular tyrosinase activity in B16F1. KAMP also showed greater antioxidant activity than KA, KAML and KAMO as measured in anti-lipid peroxidation method and other antioxidant assay.

Evaluation of the depigmenting activity of KA esters by *in vivo* model using zebrafish embryo indicated that KAMP has better depigmenting activity than KA and KAMO. The toxicity level of KA and KA esters were also estimated where KAMP gave lower toxic effect compared to KA, KAML and KAMO, as evaluated using B16F1 cells, G361 cells and zebrafish embryo. Zebrafish embryo treated with KAMP also showed higher survival rate, high hatchability, stable heart-beat rate and no significant teratogenic effect as compared to KAML.

The results from this study have demonstrated that KA esters can be synthesized in solvent-free system as an alternative to solvent system. Solvent-free system has advantage of using chemical at low cost and environmental friendly process. Large scale production of KA esters could be performed using STR and FR, where the yield could be further improved by the improvement of mixing condition and optimization of the process variables. The absence of toxic and better depigmenting effect of KA esters as compared to KA suggest that KA esters are safe to be applied as skin-whitening agents in commercial cosmetic formulation.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PENGHASILAN ASID KOJIK ESTER SECARA ENZIMATIK DAN ANALISIS NYAH-PIGMEN DENGAN MENGGUNAKAN MODEL *IN VITRO* DAN *IN VIVO*

Oleh

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Asid kojik (KA) merupakan agen pemutih yang biasa digunakan di dalam pelbagai produk kosmetik. Walaubagaimanapun, KA tidak larut minyak yang menyebabkan sukar untuk diformulasikan dalam kosmetik. Oleh itu, KA ester menjadi pilihan untuk produk kosmetik. Di dalam kajian yang terdahulu, penghasilan KA ester dilakukan dengan menggunakan pemangkin kimia. Penggunaan pemangkin kimia adalah tidak mesra alam dan lebih membahayakan pengguna berbanding pemangkin biologi. Penghasilan KA ester secara enzimatik telah dikaji dan dilakukan di dalam pelbagai jenis reaktor seperti tangki reaktor bergerak (STR), reaktor lapisan terpadat (PBR) and reaktor terangkat (FR) dengan menggunakan lipase tersekatgerak komersial, iaitu lipozim TLIM, RMIM and N435, dimana keberhasilan mereka dibandingkan. Kaedah alternatif (pelarut dan tanpa pelarut) untuk penghasilan KA ester di dalam pelbagai reaktor juga dikaji. Pelbagai parameter enzimatik dan operasi reaktor diubah-suai dengan tujuan untuk menyelesaikan pelbagai masalah di dalam operasi reaktor enzim seperti kesan ricih dan potensi penggunaan semula lipase. Sifat fizikal, kimia dan nyah-pigmen aktiviti oleh KA ester dengan menggunakan pelbagai kaedah juga dikaji. Nyah-pigmen aktiviti oleh asid kojik ester telah dianalisis dengan model *in vitro* dan *in vivo* menggunakan B16F1 dan embrio ikan zebra.

Bagi esterifikasi dengan lipase N435, penghasilan KA ester yang sangat tinggi (sehingga 50%) dapat disintesis di dalam STR berbanding PBR dan FR. Enzimatik esterifikasi KA ester di dalam STR adalah alternatif yang terbaik walaupun terdapat beberapa kelemahan berbanding dengan reaktor lain. Sistem tanpa pelarut mungkin boleh dijadikan alternatif untuk penghasilan KA ester tetapi suhu yang tinggi diperlukan untuk mencairkan asid lemak tepu (asid palmitik dan asid laurik). Apabila kulit terdedah kepada sinaran ultraungu (UV), warna kulit akan berubah menjadi gelap disebabkan meningkatnya hormon alpha-melanocyte (α-MSH) dan proses oksidasi. Kajian terhadap hiper-pigmen B16F1 yang telah diransang oleh α-MSH menunjukkan asid kojik palmitik (KAMP) mempunyai inhibitasi yang tinggi terhadap penghasilan melanin berbanding dengan menggunakan KA, asid kojik laurik (KAML) dan

asid kojik oleik (KAMO). Pengurangan penghasilan melanin di dalam B16F1 yang telah dirawat bersama KAMP, berkadar lansung dengan pengurangan aktiviti tyrosinase cendawan dan tyrosinase seluler di dalam B16F1. Di dalam kajian ini, KAMP juga menunjukkan kesan antioksida yang tinggi berbanding KA, KAML and KAMO sebagaimana telah dinilai menggunakan kaedah anti-perosidasi lipid dan kaedah yang lain.

Penilaian terhadap keberkesanan nyah-pigmen oleh KA ester menggunakan model *in vivo* iaitu embrio ikan zebra menunjukkan bahawa KAMP memiliki aktiviti nyah-pigmen yang lebih baik daripada KA and KAMO. Tahap toksik KA dan KA ester juga dinilai dan KAMP menunjukkan tahap toksik yang lebih rendah daripada KA, KAML and KAMO, sepertimana telah dinilai dengan menggunakan sel B16F1, sel G361 dan embrio ikan zebra. Embrio ikan Zebra yang dirawat dengan KAMP juga menunjukkan kadar hidup yang tinggi, kadar penetasan yang tinggi, kadar denyutan jantung yang stabil dan tiada kesan teratogen berbanding KAML.

Keputusan dari kajian ini menunjukkan bahawa KA ester boleh disintesis di dalam sistem tanpa pelarut sebagai alternatif kepada sistem dengan pelarut. Sistem tanpa pelarut mempunyai kelebihan dari segi pengurangan kos dan lebih mesra alam. Produksi berskala besar boleh dilakukan dengan menggunakan sistem STR dan FR, dimana penghasilan KA ester boleh ditambah baik dengan mengoptimalkan parameter dan keadaan sebatian campuran. Ketiadaan kesan toksik dan peningkatan aktiviti nyah-pigmen oleh KA ester berbanding KA membolehkan KA ester digunakan di dalam ramuan kosmetik sebagai agen pemutih yang lebih selamat dan berkesan.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

α-MSH	alpha-melanocyte stimulating hormone
BCR	Bed column reactor
BHA	Butylhydroxyanisole
BHT	Butylhydroxytoluene
BSA	Bovine serum albumin
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
DHI	Dihydroxyindole
DHICA	Dihydroxyindole-2-carboxylic acid
DMEM	Dulbecco's modified Eagle's medium
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DOPA	L-3,4-dihydroxyphenylalanine
DOT	Dissolve oxygen tension
DPPH	2,2-diphenyl-1-picrylhydrazyl
DSC	Differential Scanning Calorimetry
EDTA	Ethylenediaminetetraacetic acid
EGF	Epidermal growth factor
ERK	Extracellular signal-regulated kinase
FBR	Fluidized bed reactor
$FeCl_3$	Iron(III) chloride
FTIR	Fourier transform infrared spectroscopy
FR	Fluidized reactor
FRAP	Ferric reducing antioxidant power
GCMS	Gas Chromatography Mass Spectrometry
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HSQC	Heteronuclear single-quantum correlation spectroscopy
H_2O_2	Hydrogen peroxide
IBMX	Isobutylmethylxanthine
JNK	c-Jun N-terminal kinase
KA	Kojic acid
KAMO	Kojic acid monooleate
KAML	Kojic acid monolaurate
KAMP	Kojic acid monopalmitate
MC1R	Melanocortin receptor
MITF	Microphthalmia-associated transcription factor
Msg1	melanocyte-specific gene 1
NMR	Nuclear magnetic resonance
N435	Novozyme 435
PBR	Packed bed reactor
PKA	Protein kinase A
PTU	1-phenyl-2-thiourea
RMIM	immobilized lipase from *Rhizomucor miehei*
RPA	Reducing power ability
SDS-PAGE	Sodium dodecyl sulfate- polyacrylamide gel electrophoresis
STR	Stirred tank reactor
TBA	Thiobarbituric acid

TBARS	Thiobarbituric acid reactive substances
TCA	Trichloroacetic acid
TGA	Thermogravimetric Analysis
TLIM	Lipozyme *Thermomyces lanuginosus* lipase
TPTZ	2,4,6-tri(2-pyridyl)-s-triazine
UATR	Universal Attenuated Total Reflectance

CHAPTER 1

INTRODUCTION

Kojic acid (KA) is produced by various *Aspergillus* and *Penicillium* species such as *A. flavus, A. parasiticus and P. rubrum* (Wei et al., 1991; Parrish et al., 1966). KA producing strains, *A. flavus*, can be improved by the monospore isolation and mutation methods to obtain a stable monokaryotic strain capable of producing high amount of KA (Madihah et al., 1996; Ariff et al., 1996; Rosfarizan et al., 1998). The optimal dissolved oxygen tension (DOT) control strategy for KA fermentation by *A. flavus* for KA production in STR has been proposed by Rosfarizan et al., (2002). In this DOT control strategy, DOT was controlled at high level (>80%) during active growth phase and then switched to low level (30%) during production phase in batch submerged fermentation to give the highest yield and overall productivities. Proposed pathway for KA biosynthesis is shown in Figure 1.1 (Bajpai et al., 1981).

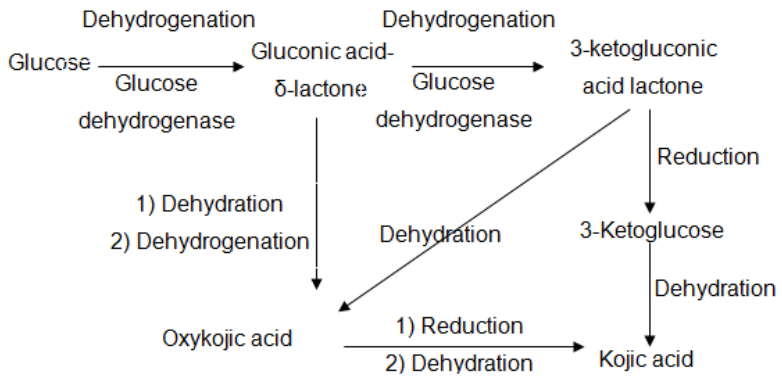

Figure 1.1. Biosynthetic pathways for kojic acid biosynthesis in *A. flavus*

KA has a wide range of industrial application such as to treat problems related to oxidation, photodamage, hyperpigmentation and skin wrinkling (Wright et al., 2014; Kotyzová et al., 2004). Hydrophilic property of KA has restricted its application in cosmetic, oily food and pharmaceutical products (Mohamad et al., 2010). KA has also been criticized for weak depigmenting effect and unstable for long storage. Moreover, there are concerns of its toxicity, carcinogenicity and hepatocarcinogenicity (Chusiri et al., 2011).

To improve KA characteristic, various KA derivatives such as KA esters have been synthesized. In industry, KA ester was developed and produced via chemical process which is not environmentally friendly (Manosroi et al., 2005; Radzi et al., 2011). A new synthesis approach using enzymatic process where cost and the use of hazardous chemical can be reduced or minimized has been developed (Chaibakhsh et al., 2009). Unlike chemical process using chemical catalyst, immobilized lipase is susceptible to inhibition, which therefore require an appropriate bioreactor design, mode of operation, substrate supply, efficient

product removal, reuse of immobilized lipase, scale-up and process control (Chaibakhsh et al., 2010). KA can be esterified into a more stable form using lipase with aims of producing better depigmenting effect. The implementation of lipase-based ester production in solvent system has been carried out using as lipase of *Candida antarctica* B lipase and lipase of *Thermomyces lanuginosus* (Noureddini et al., 2005; Adachi and Kobayashi, 2005; Noureddini et al., 2002). However, report on the production of KA esters in solvent-free system is still lacking. Solvent-free system offer several advantages over solvent system such as simplification of experimental procedure, reduce cost of chemical, reduce by-product to increase rate of reaction and reduce pollution (Singh and Chowdhury, 2011).

So far, research on enzymatic production of KA ester was only conducted in a small tube or shake flask where reports on the use of reactor system which can be scaled-up, for the production of KA esters are lacking (Ashari et al., 2009; Liu and Shaw, 1998). Stirred tank reactor (STR) is a typical mixing type reactor which is a commonly used in laboratory and industrial scales due to ease of fabrication and construction, maintenance and operation (Halim et al., 2009). Packed bed reactor (PBR) is a typical plug flow reactor. PBR provides a larger reacting surface area per unit volume than STR and is often applied in continuous process with high volumetric productivity (Balcáo et al., 1996; Rahman et al., 2011; Dahlan et al., 2005).

In order for KA ester to be commercialized, their safety and efficiency as whitening agent is necessary to be analyzed and determined. *In vitro* method is the easiest way to evaluate depigmenting effect of KA esters, which can be done using simple mushroom tyrosinase assay (Kaatz et al., 1999). As auto-oxidation was involved in melanin production, it is necessary to evaluate the antioxidant assay of KA esters (Jean et al., 2013; Costin and Hearing, 2007). This can be done using various antioxidant assay such as FRAP, and DPPH assays (Saha et al., 2008). However, these evaluations are not adequate and require *in vitro* cells model assessment as supporting data. Examples of *in vitro* models include B16 cells, G361 cells and A376 cells (Kang et al., 2009; Sato and Toriyama, 2009). The *in vitro* model using B16 cells gives some advantages over simple *in vitro* mushroom tyrosinase assessment as it allow investigation at cellular and molecular levels (Kim et al., 2003). In addition to *in vitro* model, further experiment on animal *in vivo* model is often carried out to confirm the previous findings using *in vitro* model (Akhtar et al., 2014; Oliveira at al., 2010). *In vivo* models allow the assessment of organ physiology and morphology, as well as organ-specific cell-to-cell interactions (Gonçalez et al., 2013; da Silva et al., 2013). Although KA and KA esters have been produced industrially and commercialized, the question of safety is still not fully answered. Therefore, the appropriate methodology for evaluation of KA and KA esters in term of its safety for use in cosmetic and pharmaceutical formulation shall be developed.

Therefore, the objectives of this study were

1. To investigate the influence of various bioreactor designs and parameters on the performance of the enzymatic esterification of KA and fatty acid to various KA esters (KA monooleate, KA monolaurate and KA monopalmitate) using commercial lipases in solvent and non-solvent systems.

2. To evaluate the depigmenting effect of KA esters, produced by the enzymatic esterification, in hormone-stimulated hyper-pigmented B16F1 melanoma cells using *in vitro* models

3. To evaluate anti-oxidant properties of KA esters, produced by the enzymatic esterification, to free radicals involved in pigmentation process

4. To evaluate the hypopigmenting, toxic and teratogenic effect of KA esters, produced by the enzymatic esterification, using *in vivo* animal model with zebrafish embryo

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