OVER-EXPRESSION OF FabA, FabB, AND FabF FROM Photobacterium marinum J15 FOR ENHANCEMENT OF OMEGA-7 MONOUNSATURATED FATTY ACID PRODUCTION IN Escherichia coli

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FBSB 2018 64

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

November 2018

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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November 2018

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Omega-7 monounsaturated fatty acids comprising of palmitoleic acid (16:1ω7) and its elongation product *cis*-vaccenic acids (18:1ω7) are increasingly attracting scientific attention due to their multiple values in human health, industrial chemicals, and biodiesel formation. Conventionally, plants, animal fat products, vegetable and marine oil have been described to be the major sources of omega-7 fatty acids. However, all these natural sources provide a limited commercial quantity of these fatty acids. Besides, the chemical synthesis of these fatty acids bring about low efficiency and frequently requires harsh reaction conditions, prolonged times, and use of expensive equipments. Marine bacteria such as *Photobacterium* spp. contain omega-7 monounsaturated fatty acids in their membrane phospholipids which enable them to preserve their membrane fluidity. Considering the limited availability of these valuable fatty acids and other aforementioned problems associated with the other synthesis routes, developing metabolic strategies for enhancing the production of omega-7 fatty acids is of utmost importance. The main aim of this research was to enhance the production of omega-7 monounsaturated fatty acid in *E. coli*. In order to achieve that, fatty acids profile of *P. marinum* J15 and its biosynthesis pathway were determined. Three fatty acids genes designated as *fabA*, *fabB*, and *fabF* were amplified from *P. marinum* J15 genome. The genes were cloned and over-expressed individually and in combinatorial in *E. coli* BL21(DE3) to investigate their effects on the omega-7 fatty acids content. Effects of growth temperature on fatty acids content in recombinant *E. coli* were also studied. GC-MS analysis revealed the wild-type *P. marinum* J15 produced 51.6% of omega-7 fatty acids (36.3% of palmitoleic acid and 15.3% of vaccenic acid) after incubation at 20 °C. Fatty ac id biosynthesis pathway in *P. marinum* J15 contains 13 distinct proteins; 3 proteins (FabK, FabV, and FabY) are not commonly found in *E. coli.* Single over-expression of FabB in *E. coli* BL21(DE3) at 15 °C enhanced the omega-7 fatty acids by 3. 3 fold (53.9% of the total fatty acids). Meanwhile, single over-expression of FabA and FabF in *E. coli*

BL21(DE3) enhanced omega-7 fatty acids only by 1.4 (23.1% of TFAs) and 1.6 (26.0% of TFAs) fold following incubation at 15 °C. Among the three genes, *fabB* showed the highest effect in the enhancement of omega-7 fatty acids, whereas *fabA* and *fabF* showed the lowest effect. Overexpression of *fabA* was important for increasing the amount of palmitic acids. Overexpression of the *fabABF* in *E. coli* BL21(DE3) enhanced the omega-7 fatty acids by 3.9 fold (70% of the total fatty acids) upon incubation at 20 °C. Incubation of the cells at lower growth temperature has been shown to increase the production of omega-7 fatty acids. In conclusion, this research may set the foundation for initiating new strategies to develop *E. coli* platforms devoted for large-scale production of omega-7 fatty acids.

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

PENGUNGKAPAN SECARA BERLEBIHAN FabA, FabB, DAN FabF DARIPADA *Photobacterium marinum* J15 UNTUK MENINGKATKAN PRODUKSI ASID LEMAK TAK TEPU OMEGA-7 DI DALAM *Escherichia coli*

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Asid lemak tak tepu omega-7 yang terdiri daripada asid palmitoleik (16:1ω7) dan dari produk pemanjangan asid *cis*-vasenik (18:1ω7), semakin mendapat perhatian dalam bidang saintifik kerana kesan mereka kepada kesihatan manusia, perindustrian kimia, dan penghasilan biodiesel. Tumbuh-tumbuhan, produk lemak haiwan, sayuran dan minyak laut adalah sumber utama asid lemak omega-7 yang diperoleh secara konvensional. Walau bagaimanapun, semua sumber semulajadi ini menghasilkan asid lemak dalam kuantiti yang terhad bagi pengkomersilan. Selain itu, pensintesisan asid lemak secara kimia memberi keberkesanan yang rendah dan juga sering memerlukan keadaan yang ekstrem bagi tindak balas, penambahan dari segi masa, dan memerlukan penggunaan peralatan yang mahal. Bakteria marin seperti *Photobacterium* spp. mengandungi asid lemak tak tepu omega-7 di dalam membran fosfolipid mereka yang membolehkan pengekalan kelembapan pada membran tersebut. Dengan keterbatasan bagi perolehan asid lemak dan masalah lain yang berkaitan dengan jalan pensintesisan, strategi dari segi metabolik untuk meningkatkan pengeluaran asid lemak omega-7 adalah sangat penting. Tujuan utama penyelidikan ini adalah untuk meningkatkan pengeluaran asid lemak tak tepu omega-7 dalam *E. coli*. Profil asid lemak *P. marinum* J15 dan laluan biosintesisnya telah ditentukan bagi mencapai tujuan itu. Tiga gen asid lemak yang ditakrifkan sebagai *fabA, fabB,* dan *fabF* telah diamplifikasi dari genom *P. marinum* J15. Gen-gen tersebut telah diklon dan diungkapkan secara individu dan secara kombinasi dalam *E. coli* BL21(DE3) untuk menyiasat kesan mereka terhadap kandungan asid lemak omega-7. Kesan suhu pertumbuhan kepada kandungan asid lemak dalam *E. coli* rekombinan juga telah dikaji. Analisis GC-MS menunjukkan *P. marinum* J15 jenis liar menghasilkan 51.6% asid lemak omega-7 (36.3% adalah asid palmitoleik dan 15.3% adalah asid vaksin) selepas inkubasi pada 20 °C. Laluan biosintesis asid lemak dalam *P. marinum* J15 mengandungi 13 protein yang berbeza; 3 protein (FabK, FabV, dan FabY) yang tidak selalu dijumpai dalam *E. coli*.

Pengungkapan FabB dalam *E. coli* BL21 (DE3) pada 15°C telah meningkatkan asid lemak omega-7 sebanyak 3. 3 kali ganda (53.9% daripada jumlah asid lemak). Sementara itu, FabA dan FabF dalam *E. coli* BL21(DE3) hanya meningkatkan asid lemak omega-7 sebanyak 1.4 ganda (23.1% daripada TFAs) dan 1.6 ganda (26.0% daripada TFAs) dengan inkubasi pada 15 °C. Antara tiga gen, FabB menunjukkan impak terbesar dalam peningkatan asid lemak omega-7, sedangkan FabA dan FabF menunjukkan kesan paling rendah. Pengungkapan berlebihan FabA adalah penting untuk meningkatkan jumlah asid palmitik. Pengungkapan berlebihan FabABF dalam *E. coli* BL21(DE3) meningkatkan asid lemak omega-7 sebanyak 3.9 kali ganda (70% daripada jumlah asid lemak) setelah inkubasi pada 20°C. Inkubasi sel pada suhu yang lebih rendah telah menunjukkan peningkatan pengeluaran asid lemak omega-7. Kesimpulannya, penyelidikan ini dapat menyediakan asas untuk memulakan strategi baru untuk *E. coli* sebagai platform yang dikhususkan untuk pengeluaran asid lemak omega-7 bagi skala besar.

ACKNOWLEDGEMENTS

It gives me a great pleasure to thank to almighty God for given me the opportunity, wisdom, zeal and good health to successfully complete my PhD programme in the field of genetic engineering and molecular biology at the Faculty of Biotechnology and Biomolecular Science, Universiti Putra Malaysia.

First of all, I would like to convey my most sincere gratitude to Dr. Suriana Sabri as the chairman of my supervisory committee for her continuous advices, invaluable support, guidance, and care to see the successful conduct of this research despite the multiple challenges. I really appreciate her immense contribution, and I pray that may God continue to show mercy on her ways.

I would also like to express my gratitude to members of my supervisory committee including Professor Dr. Raja Noor Zaliha biti Raja Abdul Rahman and Assoc. Professor Dr. Mohd Shukuri Mohamad Ali for their great contribution toward to the smooth conduct of this research, may God continue to bless them and may He light all their ways of achievement.

My sincere gratitude goes to my late father Alhaji Musa Moi and my mother Hajiya Hauwa for their prayers, love, care, support, and generosity. May Allah grant them all with his best jannautul firdaus. My gratitude also goes to the entire members of my family for their encouragement, advices and support as well, may Allah bless them all. I extend my sincere thanks to my wife for her uncountable contribution toward to the success of this research, may Allah bless her abundantly.

I am immensely thankful to all the principal investigators at Enzyme and Microbial Technology Research Centre (EMTEch) who's their expertise, knowledge, wisdom, and understanding added a great value to the conduct of this research. I wish to express my sincere gratitude to my lab mates in the Protein Engineering lab, Lab 140 (Biotech 2) and Institute of Bioscience (IBS), for their support, assistance and cooperation.

Finally, I would also like to acknowledge the continuous care and valuable financial support from the management of Bauchi State University Gadau, Bauchi State, Nigeria. I am really grateful for giving me the opportunity to participate in the study fellowship training.

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABREVIATIONS

α	Alpha
β	Beta
°C	Degree celsius
%	Percentage
A600nm	Optical density at wavelength of 600 nanometer
µL	Microliter
µm	Micrometer
mM	Millimolar
mL	Millilitre
h	Hours
min	Minute
sec	Second
rpm	Revolution per minute
ORF	Open reading frame
APS	Ammonium persulfate
ATP	Adenosine triphosphate
bp	Base pair
CaCl2	Calcium chloride
KCl	Potassium chloride
MgSO4	Magnesium chloride
HCl	Hydrochloric acid
DNA	Deoxyribonucleic acid

EC	Enzyme Commission
EDTA	Ethylenediaminetetraacetic acid
LB	Luria-Bertani
IPTG	Isopropyl β-D-1-thiogalactopyranoside
ddw	Deionised distilled water
SDS	Sodium dodecyl sulphate
TEMED	N, N,N,N-Tetramethyllenediamade
TBS	Tris-buffered saline
TBS/T	Tris-buffered saline/tween
BCIP-T	5-bromo-4-chloro-3-indolyl phosphate/ tween
SDS-PAGE	Sodium dodecyl sulphate polyacrylamide gel electrophoresis
FAMES	Fatty acids methyl esters
GCMS	Gas chromatography mass spectrometry
FFAs	Free fatty acids
FAS	Fatty acid synthesis
TFAs	Total fatty acids
HDL	High density lipoprotein
LDL	Low density lipoprotein
MUFA	Monounsaturated fatty acid
PUFA	Polyunsaturated fatty acid
SFA	Saturated fatty acid
USF	Unsaturated fatty acid
LLDPE	Low linear density polyethylene

ACC	Acetyl-CoA Carboxylase
FabA	β-Hydroxydecanoyl-ACP dehydrase/isomerise
FabB	β-Ketoacyl-ACP synthase I
FabD	Malonyl-CoA:ACP transacylase
FabF	β -Ketoacyl-ACP synthase II
FabG	β -Ketoacyl-ACP reductase
FabH	β -Ketoacyl-ACP synthase III
FabI	Enoyl-ACP reductase I
FabL	Enoyl-ACP reductase II
FabK	Enoyl-ACP reductase III
FabV	Enoyl-ACP reductase IV
FabY	β -Ketoacyl-ACP synthase III
FabZ	β -hydroxyacyl-ACP dehydrase
ENRs	Enoyl-ACP reductases
NADPH	Nicotinamide adenine dinucleotide phosphate
SDR	Short-chain dehydrogenase reductase
TIM	Flavin-containing triosephosphate isomerase
MCS	Multiple cloning site
BBH	Bidirectional Best Hit
RT	Room temperature
TAE	Tris-acetic-EDTA
NCBI	National center for biotechnology information
EMBL	European Molecular Biology Laboratory
EBI	European Bioinformatics Institute

CHAPTER 1

INTRODUCTION

1.1 Introduction

Omega-7 fatty acids including palmitoleic acid (C16:1ω7) and its counterpart *cis*-vaccenic acid (C18:1ω7) are highly attractive compounds nowadays due to their wide applications in pharmaceuticals, nutraceuticals, foods and chemicals (Wang et al., 2016; Wu et al., 2012). Accumulated evidence from studies has proven that omega-7 fatty acids could increase cell membrane fluidity, reduce inflammation, aid in the management of cardiovascular disease and prevention of oncogenesis (Maedler et al., 2003; Mozaffarian et al., 2010; Welters et al., 2006). Moreover, clinical findings have identified that omega-7 fatty acids could improve insulin sensitivity, manage body weight, and normalize abnormal lipid profile (including raising beneficial HDL-cholesterol) (Dimopoulos et al., 2006; Lu et al., 2012; Yang et al., 2011; Yang et al., 2013). In addition to their biological role in human, omega-7 fatty acids also contribute immensely to industrial application especially in the area of biodiesel formation, polymer precursor production and as well as cosmetics formulation (Nguyen et al., 2015; Wu et al., 2012). Omega-7 fatty acids also have been considered valuable for the production of 1-octene which is used commercially as a monomer in the production of polyethylene, including low linear density polyethylene (LLDPE) (Meier, 2009; Rybak et al., 2008; del Cardayre, 2013).

Conventionally, plants, animal fat products, vegetable and marine oil have been described to be the major sources of omega-7 fatty acids. However, all these natural sources supply limited commercial quantity of these fatty acids (Kolouchová et al., 2015; Shinde et al., 2013). Meanwhile, synthesizing these fatty acids by chemical means causes low productivity and usually requires noisy reaction environments, lengthy time, and involves high cost of apparatus (Yu et al., 2014). As the benefits of omega-7 fatty acids have been thoroughly discovered and proven, the demands for these fatty acids will substantially increase, therefore, seeking for a new alternative high in omega-7 fatty acids composition and unbounded by seasonal and regional factors becomes the number one choice to solve the problem of insufficient supply of these valuable fatty acids.

P. marinum J15 is a marine bacterium isolated from marine water at Tanjung Pelepas, Johor (Roslan et al., 2016). This type of species is known to possess omega-7 fatty acids (reviewed in Moi et al 2017). The omega-7 fatty acids are important for the maintenance of their membrane fluidity (Allen et al., 1999; Allen and Bartlett, 2000). The genome sequence of *P. marinum* J15 has been determined (Roslan, et al., 2016). Nonetheless, the fatty acids biosynthesis pathway and the fatty acid profile in this bacterium have not been investigated.

Omega-7 fatty acids are produced *via* the anaerobic pathway in bacteria. This pathway does not require the use of oxygen and is totally dependent on the enzymes to introduce double bond into saturated compounds prior to elongation through the normal fatty acid biosynthesis mechanism (Altabe et al., 2013; Altabe et al., 2007; Bi, 2016). Basically, there are three important enzymes that involve in the synthesis of omega-7 fatty acids; FabA (β-hydroxydecanoly-ACP dehydrase) encoded by the *fabA*, FabB (β- ketoacyl-ACP synthases I) encoded by *fabB*, and FabF (β- ketoacyl-ACP synthases II) encoded by *fabF* (Cao et al., 2010; Garwin et al., 1980a). Cloning and over-expression of *fabA* and *fabB* from *E. coli* strain have shown to increase the composition of vaccenic acid in *E. coli* BL21(DE3) (Cao et al., 2010). In *E. coli* FabA, FabB and FabF are essential for the production of unsaturated fatty acids; FabA catalyzes the initial steps in the formation of unsaturated fatty acid while FabB and FabF perform the elongation steps (Garwin et al., 1980a; Lu et al., 2004).

Considering the limited availability of these valuable fatty acids and other aforementioned problems associated with the other synthesis, metabolic engineering of omega-7 fatty acids in *E. coli* is the most promising approach for enhancing the production.

1.2 Research objectives

The main aim of this project is to enhance the production of omega-7 fatty acids in *E. coli* by heterologous overexpression of fatty acid synthesis pathway genes from *P. marinum* strain J15. The specific objectives of this research are:

1. To determine the fatty acid profile and the genes involved in fatty acids biosynthesis pathway of *P. marinum* strain J15 at different temperature.
2. To clone fabA, *fabB*, and *fabF* from *P. marinum* strain J15 into *E. coli.*
3. To determine the effects of single over-expression and co-overexpression of FabA, FabB, and FabF in *E. coli* towards the enhancement of omega7-fatty acids.

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