OPTIMIZATION OF BIOCONVERSION OF R-(+)-LIMONENE TO R-(+)-α-TERPINEOL BY FUNGI IN EMULSION SYSTEM USING RESPONSE SURFACE METHODOLOGY

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DOCTOR OF PHILOSOPHY
UNIVERSITY OF PUTRA MALAYSIA

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DEDICTION

A Specially dedication

To my wife Firouzeh and my son Sepanta all their love, care, support, and believe in me

Abstract of thesis presented to the Senate of University Putra Malaysia in fulfillment of
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Chairman: Professor Dzulkefly Kuang Abdullah, PhD

Institute: Institute of Bioscience

R-(+)-limonene is a non expensive by product of the citrus industry and it is a potential starting compound for bioconversion to fine chemicals. Chemical synthesis was used for α-terpineol production from limonene, but in this process unwanted isomers or substances were produced and generated large amounts of waste. In this study, a new method of bioconversion of R-(+)-Limonene to R-(+)-α-terpineol by seven fungi was investigated in emulsion systems which were prepared by mixing oil, Tween 80 and Potato Dextrose Broth (PDB). R-(+)-limonene was dissolved in oil phase and fungi were added into an aqueous phase. Optimization study for the best emulsion system stability was done by Design Expert 7 for three oils; decane, cyclohexane and tetradecane. The fungi were adapted 10 times to obtain strong fungi before bioconversion study. The α-terpineol yield was extracted by hexane and subsequently quantified by GC-FID. After 72 hours of bioconversion reaction using adapted fungi with 1% (w/v) R-(+)-limonene, 30% decane (v/v) and 1% tween 80 (w/v) in emulsion system at desired temperature and 160 rpm, the best yields were 176, 31.2, 29.6, 107.1, 96.6, 141.7 and 402.4 mg/100 ml for *A. terreus ATCC 10029, A. niger ATCC 200345, F. oxysporum ATCC 11137, F. oxysporum CBS 620.87, P. purpurogenome PTCC 5212, P. digitatum ATCC 201167* and *A. niger K8* respectively. After media components optimization that affects the fungal growth (carbon and nitrogen sources), the bioconversions were again tested by seven fungi. Final yields were 701, 133.1, 71.8, 239.6, 155.9, 349.2, and 584.1 mg/100 ml for *A. terreus ATCC 10029, A. niger ATCC 200345, F. oxysporum ATCC 11137, F. oxysporum CBS 620.87, P. purpurogenome PTCC 5212, P. digitatum ATCC 201167* and *A. niger K8* respectively. Optimization of bioconversion study was carried out only for the best fungus *(A. terreus ATCC 10029)* that gave the highest yield in a shake flask and 2L bioreactor. After optimization of the bioconversion parameters, the best yield of α-terpinel was 812 mg/100 ml for *A. terreus ATCC 10029* using a shake flask. This result is about three times higher than the previously reported value (3.2 gm/l). The bioconversion studies were also carried out in emulsion systems using cyclohexane and tetradecane under the optimum conditions. The best yield using cyclohexane was 133 mg/100 ml for *A. terreus ATCC 10029* and the best yield for tetradecane systems was 670 mg/100ml for *Asp. niger K8*. Effects of different percentage of oil phase (10%, 20% and 30% of decane, cyclohexane and tetradecane) on yields were also evaluated and it was found that the best oil for bioconversion of R-(+)-limonene to R-(+)-α-terpineol was 30% decane.

Using emulsion system for bioconversion is feasible because it provides a good medium for direct interaction between fungi and substrate. Using decane (Log $P_{O/W}$: 6.25) as oil phase in emulsion help to decrease limonene (Log $P_{O/W)}$: 4.8) toxicity toward fungi. Terpineol yields were increased after adaptation of fungi by limonene and optimization of media components. Optimization of bioconversion parameters provided new condition for *A. terreus* to produce more terpineol. Two another oils, cyclohexane (Log $P_{O/W}$: 3.4) and tetradecane (Log $P_{O/W}$: 8.19) showed decrease in yield, suggesting that toxicity is a one of important parameters for bioconversion of limonene.

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

PENGOPTIMUMAN PENUKARAN BIO R-(+)-LIMONENA KAPADA R-(+)-α-TERPINEOL OLEH KULAT DALAM SISTEM EMULSI MENGGUNAKAN KAEDAH TINDAK BALAS PERMUKAAN

Oleh

MIRSASAN MIRPOUR

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Pengerusi: Profesor Dzulkefly Kuang Abdullah, PhD

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R-(+)-limonena a adalah hasil sompingan yong murah dari industry sitrus dan berpotensi sebagai bahan mula delam penukaran bio kepada bahan kimia balus. Sintesis kimia teah digunakan untuk pengeluaran α-terpineol dari limonena, tetapi dalam proses ini isomer asing atau bahan-bahan yang tidak diingini juga dihasilkan serta peningkatkan sisa. Delam kajian ini, kaedah baru penukaran bio R-(+)-limonena kepada R-(+)-α-terpineol oleh tujuh kulat telah dikaji dalam sistem emulsi yang disediakan dengan mencampurkan minyak, tween 80 dan kentang dekstrosa kaldu. R-(+)-limonena telah dilarutkan dalam fasa minyak dan kulat ditambah ke dalam fasa akueus. Kajian pengoptimuman untuk menghasilkan sistem emulsi yang stabil telah dilakukan munggunakan perisian Pakar Rekabentuk 7 untuk tiga jenis minyak; dekana, sikloheksana dan tetradecana. Kulat telah diadaptasi sebanyak 10 kali untuk mendapatkan kulat yang kuat sebelum kajian penukaran bio dilakukan. Hasil α-terpineol diekstrak menggunakan heksana dan dianalisis dengan GC-FID. Selepas 72 jam tindak balas penukaran bio menggunkan kulat teradaptasi dengan 1% (w/v) R-(+)-limonena, dekana (30% v/v) dan tween 80 (1% w/v) delam sistem emulsi pada suhu tertentu dan 160 rpm, hasil terbaik adalah 176, 31.2, 29.6, 107.1, 96.6, 141.7 dan 402.4 mg/100 ml masing-masing bagi *A. terreus ATCC 10029, A. niger ATCC 200345, F. oxysporum ATCC 11137, F. oxysporum CBS 620.87, P. purpurogenome PTCC 5212, P. digitatum ATCC 201167* dan *A. niger K8.* Selepas pengoptimuman komponen media yang mempengaruhi pertumbuhan kulat (sumber karbon dan nitrogen), sekali lagi penukaran bio diuji menggunakan tujuh kulat. Hasil terakhir adalah 701, 133.1, 71.8, 239.6, 155.9, 349.2, dan 584.1 mg/100 ml masing-masing bagi *A. terreus ATCC 10029, A. niger ATCC 200345, F. oxysporum ATCC 11137, F. oxysporum CBS 620.87, P. purpurogenome PTCC 5212, P. digitatum ATCC 201167* dan *A. niger K8.* Pengoptimuman penukaran bio dilakukan hanya untuk kulat yang terbaik (*A. terreus 10029)* iaitu yang memberikan hasil tertinggi menggunakan kelalang-goncang dan bioreactor 2L. Selepas pengoptimuman, hasil α-terpineol terbaik diperdehi adalah 812 mg/100 ml bagi *A. terreus ATCC 10029.*

Keputusan ini adalah tiga kali ganda lebih tinggi daripada nilai yang pernah dilaporkan sebelum ini (3.2 gm/l). Kajan penukaran bio turut dijalankan dalam sistem emulsi menggunakan sikloheksana dan tetradecana. Hasil terbaik menggunakan sikloheksana adalah 133mg/100 ml dihasilakan oleh *A. terreus ATCC 10029,* dan hasil yang terbaik untuk sistem tetradecana adalah 670 mg/100 ml bagi *A. niger K8.* Kesan peratusan fasa minyak yang berbeza (10%, 20% dan 30% daripada dekana, sikloheksana dan tetradecana) ke atas hasil juga dikaji dan didapati minyak terbaik untuk penukaran bio R-(+)-limonena kepada R-(+)-α-terpineol adalah 30% dekana. Menggunkan sistem emulsi untuk penukaran bio adalah terbaik kerana ia menyediakan medium untuk interaksi langsung antara kulat dan substrat. Menggunakan dekana (Log $P_{O/W}$=6.25) sebagai fasa minyak dalam emulsi membantu mengurangkan ketoksikan limonena (Log $P_{O/W}$=4.8) terhadap kulat. Hasil terpineol telah meningkat selepas adaptasi kulat oleh limonena, dan pengoptimuman media komponen. Pengoptimuman parameter penukaran bio telah dilakukan untuk *A. terreus ATCC 10029* menghasilkan lebih baryak terpineol. Dua minyak yang lain, sikloheksana (Log $P_{O/W}$=3.4) dan tetradecana (Log $P_{O/W}$=8.19) menunjukkan penurunan dalam hasil. Ini telah menunjukkan bahawa ketoksikan merupakan salah satu parameter penting untuk penukaran bio limonene.

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I certify that a Thesis Examination Committee has met on 22 November 2011 to conduct the final examination of Mirsasan Mirpour on his Doctor of Philosophy thesis entitled "Optimization of Bioconversion of R-(+)-Limonene to R-(+)-α-Terpineol by Fungi in Emulsion System by Using Response Surface Methodology" in accordance with the Universities and University College Act 1971 and the Constitution of the University of Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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This thesis was submitted to the Senate University Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Date:

DECLARATION

I hereby declare that the thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that, it has not been previously or concurrently submitted for any other degree at UPM or other institutions.

MIRSASAN MIRPOUR

Date:

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LIST OF ABBREVIATIONS

α	Alpha
ºC	Degree centigrade
µl	Microlitre (10^{-6} l)
µmole	Micromole
FID	Flame ionizing detector
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectrometry
gm	Gram
gm/l	Gram per liter
L	Liter
L/min	Liter per minute
ME	Malt Extract
Mg	Milligram (10^{-3} g)
mL	Milliliter (10^{-3} L)
Mm	Millimeter (10^{-3} m)
OD	Optical Density
PDA	Potato Dextrose Agar
PDB	Potato Dextrose Broth
rpm	Rotation per minute
SAS	Statistical Analysis System
v/v	Volume per volume
w/v	Weight per volume
YE	Yeast Extract

CHAPTER 1

INTRODUCTION

1.1 General background

Aroma is a mixture of several dozen to several hundred unstable molecules that originate from plant or animal products. These unstable molecules have some characteristics including; their molecular weight is low (MW < 400 Daltons), they have high vapour pressure at room temperature and atmospheric pressure, they reach the organ through the nasal mucus, and they have dissimilar detection thresholds and chemical structures. The natural aroma of strawberry for example, is composed of nearly 350 diverse odorant compounds such as alcohols, organic acids, esters, carbonyls, and, to a lesser extent, lactones and furans (Pandey, 2004). Table 1 show the diverse chemical categories which aroma compounds might belong to.

The term *flavour* encompasses all the sensations (odor and taste) which are perceived by the following organs: tongue, nose, and retronasal passage. The majority of aroma compounds on the market are chemically synthesized. This process leads to the formation of unwanted racemic mixtures that suppressed their odor or flavour. Meanwhile, consumers are expressing preference for natural compounds for foods, cosmetics, and products of household cleaning. This powerful consumer demand has been a source of inspiration to conduct researches into so-called natural molecules with the aim of substituting those synthesized molecules that are chemically artificial (Pandey, 2004).

Table 1.1 Common aroma compounds and their notes (Pandey, 2004).

Chemical structure	**Example**
Alcohols	Isoamyl alcohol (fuel oil, whiskey) 1-Octen-3-ol (mushroom aroma)
Carbonyls (ketones, diketones, and aldehydes)	2-Pentanone (Roquefort flavor) 2,3-Butanedione (buttery, nutlike) Benzaldehyde (bitter almond)
Carboxylic acids	Oleic acid (olive oil) Hexanoic acid (coconut oil)
Esters	Ethyl butyrate (pineapple) Ethyl isovalerate (apple on dilution)
Lactones	4-Octalactone (coconut), 4-decalactone (peach)
Terpenes	Citronellol (roselike, fresh), Menthol (mint)
Pyrazines	2-Methoxy-3-isopropylpyrazine (musty, potatolike)
Ethers	trans-Anethole (anise)
Others	3-Methyl-2-cyclopenten-2-ol-1-one (caramel-like) Eugenol (spicy, cloves) Vanillin (vanilla)

There are plentiful amounts of flavor and fragrance compounds in nature. These compounds can be found as part of the vital oils of diverse plants. Limonene, one of flavor and fragrance compound can be found in more than seventy diverse plants (Fenaroli *et al.*, 1995). It is a low priced monoterpene and in many cases the major components of essential oil of citrus fruits (Toniazzo *et al.*, 2006).

Limonene is a clear liquid and made up of two isoprene units. It is available in two optically active forms, S (L) and R (D). R-limonene has piney and turpentine odor like and S-limonene has orange smell (Bauer *et al.*, 1985). The anti cancer effects of limonene have been shown by many studies (Edris, 2007). It enhances liver enzymes levels engage carcinogens materials detoxifying. One of the popular systems for carcinogens omission is the Glutathione S-transferase (GST). It seems limonene can promote the GST system. Limonene treatment decreased mammary tumor growth in animals (Edris, 2007). One of the most significant products from bioconversion of limonene is terpineol. There are numerous isomers for terpineol (α, β, γ). The α-terpineol comprises of two enantiomers, R-(+)-α-terpineol with a floral characteristically lilac odor and S-(-)-α-terpineol with coniferous odor (Maróstica, 2007). These two enantiomers are extensively utilized in the flavor and fragrance industries (Bicas *et al.*, 2008). Terpineol is conventionally generated through chemical synthesis. This method produced both enantiomers. As a result, quality of the yield is diminished. The two enantiomers are affecting together and consequently there is a decrease in their fragrances.

1.2 Significance of bioconversion study

Biotransformation or bioconversion transforms particular substrates to target products through the utilization of a cell's enzymatic system or via straight exploitation of crude or purified enzymes. When the reaction takes place in one single stage (by enzyme), it is called biotransformation. However, if the reaction takes place in a number of steps, the term bioconversion will be applied (Pandey, 2004). Since this study using microorganisms to transform limonene, it is termed as bioconversion. A variety of reactions are catalysed in biotransformation or bioconversion, such as; oxidation, reduction, hydrolysis, dehydration, and formation of new C-C bonds. Using biocatalysts for the transformation of chemicals has many benefits in comparison to chemical catalysis. The advantages are; such as introduction of chirality, functionalization of chemically inactive carbons, selective modification of functional group in multifunctional molecules, and resolution of racemic mixtures.

It is feasible to generate aroma compounds in an aqueous solution or in an organic medium. But many substrates are only dissolved in organic solution hindered the interaction with microorganisms that normally remained in aqueous media. Thus, it is resulted in lower yield. To overcome this problem, the emulsion system was used for bioconversion study. In oil-in-water (O/W) emulsion system, the substrates were dispersed in small droplets. Under this condition, there are large surface area for interaction between substrate and microorganism and this would lead to higher yield.

Emulsion is a system that includes water, oil and an amphiphilic compound. An important thing of emulsion is the rate of stability. They have been proposed as carriers of some chemicals to be introduced to microorganisms. In order to make emulsion useful for biological systems, it is necessary that the emulsion is not toxic (Radomska and Dobrucki, 2000).

Commercial flavours and fragrances are produced via chemical synthesis. But, it is expensive and produced undesirable mixture of different isomers. In addition it generates huge amount of waste and, separation and purification of products are time consuming. For these reasons, final product is very expensive. In contrast, in bioconversion process using microorganisms is produced mostly single yield and it can be done by using cheap substrates.

1.3 Objectives of research

Main objective of this study is to carry out bioconversion of R-(+)-Limonene to α-terpineol by using fungi in emulsion system.

The specific objectives are:

- To prepare stable oil-in-water (O/W) emulsion system for bioconversion process.
- To adapt the fungi for bioconversion
- To optimize the growth media components for cultivation of fungi by using response surface methodology (RSM) statistic soft ware.

- To study the effects of Cyclohexane, Decane and Tetradecane on bioconversion reaction

5.2 Future prospective

Some possible works that can be performed in future on bioconversion study on limonene using microorganism are listed below:

1. Using alternative fungi and bacteria for bioconversion of limonene
2. Preparation of emulsion system using other oils base in their Log $P_{o/w}$.
3. In this study, it was used pure limonene, while, the orange peels extracts can be used too.
4. The economic feasibility of α-terpineol production using orange peels should be investigated since it was not addressed in this study.

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