

UNIVERSITI TEKNOLOGI MARA

**NAVIGATING GENETIC POLYMORPHISMS OF
CYP2C8 USING DENATURING HIGH
PERFORMANCE LIQUID CHROMATOGRAPHY
(DHPLC)**

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Thesis submitted in fulfilment of the requirements
for the degree of
Master in Science.

Faculty of Pharmacy

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Candidate's Declaration

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the result of my own work, unless otherwise indicated or acknowledged as reference work. This thesis has not been submitted to any other academic institution or non-academic institution for any other degree or qualification.

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ABSTRACT

Cytochrome P450 2C8 (CYP2C8), which was reported to be polymorphic, plays an important role in the metabolism of several therapeutically important drugs and endogenous substances. The large inter - subjects pharmacokinetics variations were therefore under the great influence of genetic polymorphism of *CYP2C8*. However, the inability to detect the genetic variation despite well known inter - subjects pharmacokinetics variabilities of CYP2C8, suggested that new variants may exist in the population or the current detection methods are not sensitive enough to detect new variants. The ability to identify the genetic variations is important to help predict the different responses in different individuals and maximise clinical drug safety. The aim of the study was to develop and validate a higher throughput screening method for detection of *CYP2C8* polymorphisms. The method would then be used to determine the genetic variations in healthy volunteers and cardiovascular patients in Malaysia. Whole blood was obtained and DNA was extracted from 200 subjects; 100 of healthy volunteers and 100 of cardiovascular patients. Each DNA sample was screened for variations using the PCR and DHPLC method developed. The method was compared with other existing method (allele specific PCR) and validated by direct sequencing. Six variants were detected using the method developed. Two of the variants were found to be novel. In comparison with healthy volunteers and cardiovascular patients (CVS), the frequency of IVS9-24 (C35322T) was lower in healthy volunteers which was 18% compared to 48.5% in CVS patients with a P value of <0.001. Meanwhile in exon 8 of *CYP2C8*, variant Ala410 (C33468T) was only detected in CVS patients with a frequency of 3%. In conclusion, we had successfully developed a higher throughput and automated method for the population study of *CYP2C8* in Malaysia. The presence of significantly higher frequencies of variant IVS -24 among the CVS patients suggests possible risk factor to CVS. However, further studies are required to confirm this finding.

TABLE OF CONTENT

CANDIDATE'S DECLARATION	ii
ABSTRACT	iii
ACKNOWLEDGMENTS	iv
TABLE OF CONTENTS	v
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF EQUATIONS	xii
LIST OF PLATES	xiii
LIST OF ABBREVIATIONS	xiv

CHAPTER 1: INTRODUCTION

1.1 Introduction	1
1.2 Statement of problems	2
1.3 Objectives of the study	3

CHAPTER 2: LITERATURE REVIEW

2.1 Single Nucleotide Polymorphisms	5
2.2 Drug Metabolising Enzyme	6
2.3 Cytochrome P450	7
2.3.1 CYP2C	9
2.3.2 CYP 2C8	9
2.4 Arachidonic Acid	17
2.4.1 Epoxyeicosatrienoic Acid	19
2.5 Detection Methods for SNPs of <i>CYP2C8</i>	20

2.5.1 Polymerase Chain Reaction (PCR)	21
2.5.2 Allele Specific PCR	21
2.5.3 Restriction Fragment Length Polymorphisms (RFLP)	22
2.5.4 Single Strand Conformation Polymorphisms (SSCP)	22
2.5.5 Denaturing High Performance Liquid Chromatography (DHPLC)	23

CHAPTER 3: MATERIALS AND METHODS

3.2	Enrolment of Cardiovascular Patients	26
3.3	Enrolment of Healthy Volunteers	28
3.4	DNA Extraction	28
	3.4.1 Solutions for DNA Extraction	28
3.5	Polymerase Chain Reaction	30
	3.5.1 Primer Design	31
	3.5.2 Reconstitution of Primers	33
	3.5.3 Preparation of Master Mix	35
	3.5.4 Calculation for Working Solutions	35
	3.5.5 PCR of <i>CYP2C8</i> Exon by Exon	36
	3.5.6 Touchdown PCR	39
	3.5.7 Optimization of PCR Process for <i>CYP2C8</i>	41
	3.5.7 (a) Annealing Temperature	41
	3.5.7 (b) Concentration of Magnesium Chloride	42
	3.5.7 (c) Concentration of DNA Polymerase	42
	3.5.7 (d) Concentration of Primers	42
3.8	Gel Electrophoresis	43
	3.8.1 Preparation of Agarose Gel	43
3.9	DHPLC	44