

UNIVERSITI TEKNOLOGI MARA

**STUDY ON THE EFFECT OF *CYP2D6*6* AND
*CYP2D6*10* ON THE EFFICACY OF DONEPEZIL
IN PATIENTS WITH DEMENTIA**

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ABSTRACT

Acetylcholinesterase inhibitor such as donepezil is the most common drug used in treating the symptoms of dementia. Genetic factor is closely associated in this topic since it may influence the efficacy and response of dementia patients toward donepezil. The genotyping test may be conducted to determine the CYP2D6 polymorphism of patients since it has been used for research purpose as well as clinical drug trials.

A nested multiplex allele-specific PCR method was used in this study to detect the CYP2D6 polymorphisms in human DNA samples. These allele-specific primers were used to permit the PCR amplification of the specific target sequences. The assay was tested on few samples of blood which were collected from group of patients with dementia in Hospital Kuala Lumpur. This PCR method successfully and accurately detected the homozygous wild-type, homozygous variant-type and heterozygous of each SNP. The genotype status was then correlated with clinical data of patient such as MMSE score to identify the changes of cognitive behaviour in this patient. The pharmacogenetics in patients with dementia may influence their responses toward donepezil because of the effects of CYP2D6 polymorphisms, especially CYP2D6*10 and CYP2D6*6.

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND STUDY

Dementia is a brain disorder in which gives the impact to the ability of a person to perform daily activities and think clearly, causing the changes in their personality and behaviour. The most common types and causes of dementia is Alzheimer's disease (AD), pursued by vascular and mixed dementia (Cacabelos & Martínez-Bouza, 2011). Over 25 million people have been affected by these prevalent forms of dementia at 2011, and estimated more than 75 million people will be at risk for the next 20 to 25 years worldwide (Cacabelos & Martínez-Bouza, 2011).

Patients who are diagnosed with dementia were usually being prescribed with acetylcholinesterase inhibitors (AChEIs). Cholinesterase inhibitors are commonly prescribed to patients with dementia, especially Alzheimer's disease (AD) in order to enhance the cholinergic activity in the brain (Jellinger, 2014). The level of acetylcholine (ACh) at the presynaptic receptor will be increased by binding and inhibiting the acetylcholinesterase (AChE), and thus counteract the low cholinergic activity marked in AD pathology (Noetzli et al., 2014). Donepezil is one of those AChEIs used as a first line treatment of mild to moderate AD, since it has been reported to be well tolerated to treat the symptoms, especially related to cognitive function in AD patients (Tsuno, 2016). Donepezil is metabolized by hepatic enzymes cytochrome P450 (CYP450) which is CYP2D6 and CYP3A4 to several metabolites