

UNIVERSITI TEKNOLOGI MARA

**CIPROXIFAN, A HISTAMINE H₃
RECEPTOR ANTAGONIST AS A
POTENTIAL THERAPEUTIC AGENT
IN ALZHEIMER'S DISEASE**

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

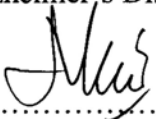
Faculty of Pharmacy

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AUTHOR'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 referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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ABSTRACT

A Histamine H₃ receptor antagonist, ciproxifan has been shown to enhance the release of neurotransmitters which play an important role in cognitive process. It is widely documented that extracellular deposition of β -amyloid peptide ($A\beta$) plays a causal role in the pathogenesis of AD. However, the role of ciproxifan on $A\beta$ has not been well documented. The present study was aimed to investigate the ability of ciproxifan to inhibit BACE-1 activity and to determine the neuroprotective effect of ciproxifan on $A\beta$ *in vitro*. Furthermore, the effect of ciproxifan on the AD related biomarkers was also investigated using APP(Sw) transgenic mice of AD model. The BACE-1 inhibition activity was carried out using BACE-1 assay kit while the SK-N-SH cells were induced with $A\beta_{25-35}$ prior to the treatment with ciproxifan and then cell viability as well as ROS assay also was determined. For *in vivo* study, ciproxifan was administrated to the mice by intraperitoneal injection (i.p) for 15 days with two selective doses (1 and 3 mg/kg) and spatial learning and memory behaviour were assessed using radial arm maze (RAM). Brain tissues were collected to measure acetylcholine (ACh), acetylcholinesterase (AChE), nitric oxide (NO), lipid peroxidation (LPO), antioxidant activities, cyclooxygenase (COX) and pro-inflammatory cytokines assay while plasma were collected to measure an anti-inflammatory cytokine TGF-1 β . The results for *in vitro* study demonstrated that ciproxifan weakly inhibited BACE-1 activity with IC₅₀BACE 500 μ g/ml and showed neuroprotective effect by increasing the cell viability and inhibited the production of ROS and these effects were comparable with positive control α -tocopherol. Meanwhile, ciproxifan significantly reduced time taken of the mouse to consume all five baits, working memory error and reference memory error in RAM. Ciproxifan did not show any alteration on the level of both $A\beta_{1-40}$ and $A\beta_{1-42}$ in APP transgenic mice. Ciproxifan also elevated the level of ACh while reduced AChE activity and showed anti-oxidant properties by reducing NO and LPO levels as well as enhancing the level of antioxidants (catalase, GSH and GPx). Moreover, the results of neuroinflammatory analysis showed that ciproxifan reduced both COX-1 and COX-2 activities, decreased the level of pro-inflammatory cytokines IL-1 α , IL-1 β and IL-6 and increased the level of anti-inflammatory cytokine TGF-1 β . In conclusion, the present study suggests that ciproxifan possessed neuroprotective effect against $A\beta$ and could protect the SK-N-SH cells from $A\beta$ -induced toxicity by preventing the cell death through the inhibition of oxidative stress. However, protective effects of ciproxifan probably were not through the inhibition of BACE-1 activity and the reduction of $A\beta$ level but by other mechanism. The ameliorative effect of ciproxifan on memory deficit of APP transgenic mice may be mediated through improving cholinergic, antioxidant and anti-inflammatory activities. This present study may provide some scientific evidences of ciproxifan through various mechanisms as a promising agent for the treatment of AD.

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TABLE OF CONTENTS

	Page
AUTHOR'S DECLARATION	ii
ABSTRACT	iii
ACKNOWLEDGEMENT	iv
TABLE OF CONTENTS	v
LIST OF TABLE	ix
LIST OF FIGURES	x
LIST OF EQUATIONS	xiii
LIST OF ABBREVIATION	xiv
CHAPTER ONE: INTRODUCTION	1
1.1 Background of Study	1
1.2 Problem Statement	2
1.3 Research Hypothesis	3
1.4 Objectives	3
CHAPTER TWO: LITERATURE REVIEW	4
2.1 Alzheimer's Disease	4
2.2 Neuropathology of AD	6
2.3 Degeneration of Cholinergic Activity	8
2.4 Oxidative Stress in Neurodegeneration	10
2.5 Nitric Oxide in Neurodegeneration	11
2.6 Lipid Peroxidation in Neurodegeneration	12
2.7 Anti-oxidant Defence System	14
2.8 Neuroinflammation in AD	15
2.9 Current Therapies for AD	18