

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

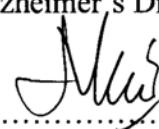
Faculty of Pharmacy

January 2015

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 (Aβ) plays a causal role in the pathogenesis of AD. However, the role of ciproxifan on Aβ 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 Aβ *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 Aβ₂₅₋₃₅ 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-1β. The results for *in vitro* study demonstrated that ciproxifan weakly inhibited BACE-1 activity with IC_{50BACE} 500 µg/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 Aβ₁₋₄₀ and Aβ₁₋₄₂ 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-1α, IL-1β and IL-6 and increased the level of anti-inflammatory cytokine TGF-1β. In conclusion, the present study suggests that ciproxifan possessed neuroprotective effect against Aβ and could protect the SK-N-SH cells from Aβ-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-1activity and the reduction of Aβ 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.

ACKNOWLEDGEMENT

First and above all, all praises and thanks to Almighty Allah for providing me this opportunity and granting me the capability to complete this thesis successfully. I would never have been able to finish this thesis without the help and guidance of several people. I would therefore like to offer my sincere thanks to all of them.

I would like to express my sincere gratitude to my supervisor Assoc Prof Dr. Vasudevan Mani for his continuous support, excellent guidance, patience, constructive comments and corrected my thesis throughout this period. Without his guidance and persistent help this thesis would not have been possible. I could not have imagined having a better advisor for my Master study. Besides my supervisor, I would like to thank my co-supervisors, Dato' Professor Dr. Abu Bakar Abdul Majeed and Assoc Prof Dr. Kalavathy Ramasamy for her assistance, suggestion and providing me with an excellence laboratory environment at CDDR (Collaborative Drug Discovery Research) Lab and also Dr Lim Siong Meng for sharing knowledge and ideas in assisting me with this project.

My special thanks also goes to my colleagues Nur Syafiqah Rahim, Nor Amalina Alwi and Nur Shamimi Azahan for helping me in my lab works, for their time and sharing knowledge throughout the completion of this study. Not to forget, my fellow teammates from Brain Research Laboratory, Siti Nor Shazwani, Aliya, Aimon Zahariah, Nazif, Khalil, Marsita, Nurul Syahida, Salme Suhana, Serene Sofea and also laboratory assistance En Syed Ridhuan for helping and managing the laboratory. Not to mention all CDDR group members, all the supportive staffs and lecturer of Faculty of Pharmacy for the guidance and assistance and all those their names do not appear here who have contributed to the completion of this study. Thanks for the support and the friendship throughout my time here making it a memorable one.

Special thanks to Minister of Science, Technology and Innovation, MOSTI (E-Science Project No. 02-01-01-SF0576) and Institute of Graduate Studies, Universiti Teknologi MARA (IPSiS) for the financial support of this project.

Finally, my deepest gratitude to my beloved family especially my parent En Jaafar bin Said and Pn Fatimah Bt Mohd Ghazali , my sisters Nor Hidayah and Nuradilah and my brother Abdul Rashid for their advice, understanding, moral and financial support and warm encouragement along these three years.

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