UNIVERSITI PUTRA MALAYSIA

NEUROPROTECTIVE PROPERTIES OF CENTELLA ASIATICA (L.) URBAN ON COMBINED D-GALACTOSE AND ALUMINIUM CHLORIDE-INDUCED TOXICITY AND COGNITIVE IMPAIRMENT IN RATS

SAMAILA MUSA CHIROMA

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By

SAMAILA MUSA CHIROMA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

July 2019

DEDICATION

This work is dedicated to my wife and children:
Dr (Mrs) Elizabeth Musa Chiroma, Ardo Musa Chiroma, Samaila Musa Chiroma and Dika Musa Chiroma.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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Chairman : Mohamad Aris Mohd Moklas, PhD
Faculty : Medicine and Health Sciences

Cognitive impairments and cholinergic dysfunctions have been well documented as a disorder in old age diseases including Alzheimer's disease (AD). D-galactose (D-gal) has been reported to be a senescence agent, while aluminium acts as a neurotoxic metal, but little is known about their combined effects on rats at different doses. The plant *Centella asiatica* (CA) has been reported to exhibit neuroprotective effects both in vitro and in vivo models of neurodegenerative diseases. Hence, the present study established AD-like rat model of neurotoxicity and cognitive impairment induced by D-gal and aluminium chloride ($AlCl_3$), besides exploring the potential protective effects of CA in the AD-like rat's model. Healthy male albino wistar rats were injected with D-gal 60 mg/kg intra peritoneally (i.p), while $AlCl_3$ (100, 200, or 300 mg/kg) was orally administered once daily for 10 consecutive weeks. Behavioural assessment, open field test (OFT) and Morris water maze (MWM) test were evaluated, along with histopathological examination of the hippocampus. Additionally, biochemical measurements of acetylcholinesterase (AChE) and phosphorylated tau protein levels (P-Tau) of the rat's brains were also evaluated. Subsequently, another batch of rats were co-administered with D-gal 60 mg/kg and $AlCl_3$ 200 mg/kg and CA (200, 400 and 800 mg/kg) and donepezil 1 mg/kg for 10 weeks. Behavioural assessments of the rats and morphological analysis (Nissl's staining and transmission electron microscopy) of their brains were carried out. Further, oxidative stress biomarkers (MDA and SOD), P-Tau and its synthetic proteins, apoptotic gene markers and AChE levels were also evaluated. The results revealed that rats treated with D-gal 60 + $AlCl_3$ 200 mg/kg showed cognitive impairments in both spatial and non-spatial learning and memory tests, associated with marked neuronal loss ($p<0.05$), oxidative stress ($p<0.05$) and increased AChE level ($p<0.05$) in their brains. Additionally, significant increase in the expression of P-Tau and GSK-3β ($p<0.05$) and decrease in the expression of PP2A ($p<0.05$) in their brains were also observed. Finally, there was also 4 folds decrease of Bcl-2 mRNA and 1.4 folds increase in the expression caspase-

3 mRNA in the rat's hippocampus. Administration of CA, and irrespective of dose alleviated the D-gal and $AlCl_3$ induced AD-like associated pathologies in rats. These includes cognitive deficits, AChE level, oxidative stress, aberrant cytoarchitecture of the rats brains, expression of P-Tau biosynthetic proteins and expression of genes associated with intrinsic mitochondria-mediated apoptosis. Thus exhibiting neuroprotective effects which could be attributed to the synergistic action of some of CA's active phytochemicals. All these findings provide scientific evidence to support the exploitation of CA as a safe and effective plant to consider in the fight against AD.

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

CIRI-CIRI NEUROPROTEKTIF *Centella asiatica* (L.) TERHADAP TOKSISITI DAN KEMEROSOTAN KOGNITIF PADA TIKUS YANG DIARUH OLEH GABUNGAN D-GALAKTOS DAN ALUMINIUM KLORIDA

Oleh

SAMAILA MUSA CHIROMA

Julai 2019

Pengerusi : Mohamad Aris Mohd Moklas, PhD
Fakulti : Perubatan dan Sains Kesihatan

Kemerosotan kognitif dan kegagalan fungsian kolinergik telah banyak dilaporkan dalam penyakit yang berkaitan dengan usia tua, seperti penyakit Alzheimer (AD). D-galaktos (D-gal) telah dilaporkan sebagai agen penuaan neuron dan aluminium bertindak sebagai logam yang bersifat neurotoksik. Walaubagaimanapun, maklumat mengenai aruhan gabungan oleh D-gal dan aluminium pada tikus untuk melihat neurotoksisiti dan kemerosotan kognitif pada dos yang berbeza adalah amat terhad. Tumbuhan *Centella asiatica* (CA) telah dilaporkan mempunyai sifat neuroprotektif pada kajian yang menggunakan model in vitro dan in vivo bagi penyakit yang berkaitan dengan kemerosotan neuron. Oleh itu, kajian ini bertujuan untuk membangunkan model tikus untuk kajian neurotoksik dan kemerosotan kognitif dengan menggunakan aruhan gabungan D-gal dan aluminium klorida (AlCl3). Kajian diteruskan untuk melihat dan meneroka ciri-ciri perlindungan neuron oleh CA pada model tikus tersebut. Tikus albino *wistar* jantan diberikan aruhan gabungan D-gal 60 mg/kg (i.p) dan AlCl3 (100, 200, atau 300 mg / kg) (oral) sekali sehari, selama 10 minggu berturut-turut. Parameter yang diukur ialah penilaian tingkah laku semasa ujian lapangan terbuka (OFT) dan ujian maze air Morris (MWM); penelitian pada perubahan histopatologi di bahagian hipokampus; pengukuran dan penilaian aktiviti biokimia asetilkolinesterase (AChE) dan protein tau terfosforilasi (P-Tau). Kajian diteruskan dengan menggunakan tikus yang diaruh oleh D-gal (60 mg/kg) dan AlCl3(200 mg/kg) untuk menerima rawatan CA (200, 400 dan 800 mg/kg) dan donepezil (1 mg/kg) selama 10 minggu. Penilaian tingkah laku tikus dan analisis morfologi (mikroskopi elektron dan pewarnaan Nissl) dilakukan pada otak tikus. Pengukuran dan analisis terhadap penanda bio tekanan oksidatif (MDA dan SOD), P-Tau dan protein sintetiknya, penanda gen apoptotik dan tahap AChE turut dinilai. Keputusan ujian menunjukkan bahawa tikus yang diaruh dengan gabungan D-gal 60 + AlCl3 200 mg/kg menunjukkan kemerosotan kognitif dan disertai dengan kehilangan neuron

yang ketara ($p<0.05$), tekanan oksidatif ($p<0.05$) dan peningkatan aktiviti AchE ($p<0.05$) di dalam otak tikus. Ia turut diikuti dengan peningkatan ketara perubahan protein P-Tau dan GSK-3β ($p<0.05$) serta penurunan ketara ekspresi PP2A ($p<0.05$). Terdapat pengurangan sebanyak empat kali ganda Bcl-2 mRNA dan peningkatan sebanyak 1.4 kali ganda ekspresi caspase-3 mRNA di dalam hipokampus tikus. Pemberian CA, tanpa mengira dos, mengurangkan gejala penyakit seperti gejala AD yang disebabkan oleh gabungan aruhan oleh D-gal dan AlCl3. Pengurangan gejala tersebut ialah kemerosotan kognitif, aktiviti AChE, tekanan oksidatif, sitoarkitektur yang aberan, ekspresi protein biosintetik P-Tau dan ekspresi penanda bio gen apoptosis yang berperantara mitokondria. Ciri-ciri neuroprotektif CA yang ditunjukkan berkemungkinan disebabkan oleh tindakbalas sebatian fitokimia aktif yang wujud dalam CA. Kesemua penemuan ini memberikan bukti saintifik untuk menyokong penggunaan CA sebagai tumbuhan yang berpotensi, selamat dan berkesan untuk merawat dan mengurangkan gejala penyakit seperti gejala AD.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Mohamad Aris Mohd Moklas, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Zulkhairi Amom, PhD
Professor,
Faculty of Pharmacy
Universiti Teknology Mara Malaysia
(Member)

Mohamad Taufik Hidayat Baharuldin, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Che Norma Mat Taib, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ROBIAH BINTI YUNUS, PhD
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School of Graduate Studies
Universiti Putra Malaysia

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Name of Member of Supervisory Committee: Professor Dr. Zulkhairi Amom

Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Mohamad Taufik Hidayat Baharuldin

Signature: _____
Name of Member of Supervisory Committee: Dr. Che Norma Mat Taib

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

α	Alpha
Δ	Delta
γ	Gamma
5-HT	5-hydroxytryptamine (Serotonin)
Aβ	Beta amyloid
AβPP	Amyloid beta precursor protein
ACh	Acetylcholine
AChEIs	Acetylcholinesterase inhibitors
AD	Alzheimer's disease
ADI	Alzheimer's Disease International
AID	Age induced dementia
AIF	Apoptosis inducing factor
ANOVA	Analysis of variance
Apaf-1	Apoptotic protease-activating factor 1
ApoE	Apolipoprotein E
ApoE2	Apolipoprotein E2
ApoE3	Apoliprotein E3
ApoE4	Apolipoprotein E4
APP	Amyloid precursor protein
APPsB	Soluble beta amyloid precursor protein
ATP	Adenosine triphosphate
AVG	Average
$A\beta_{25-35}$	Beta amyloid 25-35
$A\beta_{42}$	Beta amyloid 42

BACE-1	beta-site APP-Cleaving Enzyme-1
Bax	Bcl2-Associated X protein
BCA	Bicinchoninic acid assay
Bcl-2	B-cell lymphoma 2
BSA	Bovine serum albumin
C-99	C-terminal fragment 99
CA	*Centella asiatica*
CA1	Cornu ammonis 1
CA2	Cornu ammonis 2
CA3	Cornu ammonis 3
CA4	Cornu ammonis 4
Caspase-3	Cysteinyl aspartate specific proteinase-3
Caspase-9	Cysteinyl aspartate specific proteinase-9
Caspases	Cysteinyl aspartate specific proteinase
CAT	Catalase
cDNA	Cyclic diriboxynucleic acid
ChEIs	Cholinesterase inhibitors
CNS	Central nervous system
Cox-2	Cycloxygenase
CRP	C-reactive protein
C_T	Threshold cycles
CVD	Cardiovascular disease
Cyt c	Cytochrome c
DG	Dentate gyrus
ELISA	Enzyme-linked immunosorbent assay
ETC	Electron transport chain

FAD	Familial Alzheimer's disease
FTD	Frontotemporal degeneration
GABA	γ-aminobutyric acid
GAPDH	Glyceraldehydes-3-phosphate dehydrogenase
Glu	Glutamate
GMP	Good manufacturing practices
GOI	Gene of interest
GPx	Glutathione peroxidase
GSH	Glutathione
GSK-3β	Glycogen synthase kinase 3β
H&E	Haematoxylin and Eosin
H0-	Hydroxyl
HRP	Horseradish peroxidase
HUVEC	Human umbilical vascular endothelial cell
i.p	Intraperitoneal
IL-1	Interleukin 1
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
iNOS	Inducible nitrioxide synthase
Kg	Kilogram
LPS	Lipopolysaccharide
MAP	Mitochondrial associated protein
MAPT	Mitochondrial associated protein tau
mEPM	Modified elevated plus maze
MnSOD	Mangenase superoxide dismutase
MRI	Magnetic resonance imaging

MPT	Mitochondrial permeability transition
mRNA	Mitochondrial ribosomal nucleic acid
MWM	Morris water maze
NFTs	Neurofibrillary tangles
NFTs	Neuro fibrillary tangles
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
nm	Nanometre
NMDA	N-methyl-D-aspartate
NMDA	*N*-methyl-D-aspartate
NO	Nitric oxide
NSAIDS	Non-steroidal anti-inflammatory drugs
O2-	Superoxide
OD	Optical density
OFT	Open field test
ONOO	Peroxynitrate
ORT	Object recognition test
OXPHOS	Oxydative phosphorylation
PBS	Phosphate buffered saline
PET	Positron emission tomography
PIK3	Phosphoinositide 3-kinase
Prx	Peroxiredoxin
PSEN1	Presenilin1
PSEN2	Presenilin2
P-Tua	Phosphorylated tau
RG	Reference genes

RNA	Ribonucleic acid
ROS	Reactive oxygen species
RT-PCR	Real time polymerase chain reaction
SAD	Sporadic Alzheimer's disease
SAMP	Senescence accelerated mice
SDS	Sodium dodecyl sulphate
SEM	Standard error of mean
Smad7	Mothers against decapentaplegic homolog 7
SOD	Superoxide dismutase
SP	Senile plaques
SRed	Superoxide reductase
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid-reactive species
TGF-β	Transforming growth factor beta
TNF-α	Tumour necrosis factor alpha
Trx/TrxRed	Thioredoxin/thioredoxin reductase
TβR1-kinase	Transforming growth factor beta receptor1 kinase
USFDA	United States Food and Drugs Administration
WST-1	Water soluble tetra zolium-1
XO	Xanthine oxidase

CHAPTER 1

INTRODUCTION

1.1 Background

Alzheimer's disease (AD) is the commonest cause of dementia among the elderly population. It is an irreversible and progressive neurodegenerative disease that gradually destroys memory and cognitive functions which subsequently affects the ability to carry out day to day activities (Fischer et al., 2008; Wilson et al., 2012). The early stages of AD is characterised by short term memory loss while in its late stages it is presented by mood swing, aggressiveness, confusion, social withdrawal and long term memory loss (Waldemar et al., 2007). The pathological hallmarks of AD are progressive accumulation of intracellular twisted strands of tau protein called neurofibrillary tangles (NFTs) and extracellular deposits of fragments of beta amyloid (Aβ) protein known as senile plaques (SP) in the brain. These changes are ultimately accompanied by severe damage, death of neurons and massive synaptic loss (Alzheimers, 2016; Kamat, 2015). Apart from its multiple cognitive deficits, AD could also be defined the by disordered levels of neurotransmitters in the brain, including glutamate (Glu), acetylcholine (ACh), γ-aminobutyric acid (GABA) and serotonin (5-HT) (Prakash et al., 2015). AD can be classified based on the age of onset as either early-onset AD or late-onset AD. Early onset AD manifested roughly between the ages of 30 to 60 years which accounts for approximately 1-6% of AD cases diagnosed. The late onset AD occurs after 60 years which accounts for more than 90% of all AD cases recorded (Anand et al., 2014).

Centella asiatica (CA) is a green leafy herb that is highly valued and it has been commonly used in many traditional societies the world over as a medicinal herb since prehistoric times (Sabaragamuwa et al., 2018). CA is traditionally known for its memory enhancing abilities (Orhan, 2012), as well as for the revitalisation of nerves and brain cells (Seevaratnam et al., 2012). Its' health benefits have been reported in Ayurvedic medicine in India, Unani medicine in Sri Lanka, folk medicine in South Asian countries, Chinese traditional medicine and in African traditional medicine (Jahan et al., 2012). In all the different types of medicinal practice mentioned the applications of CA include treatment of renal failure, asthma, other respiratory problems (Jaganath & Ng, 2000), leprosy, headache (Shukla et al., 1999) wound healing and memory improvement (Soepadmo et al., 1995). Further, the ameliorative effects of CA on arsenic-induced oxidative stress in rats (Flora & Gupta, 2007) and lead induced toxicity in rats (Sainath et al., 2011a) have also been documented.

1.2 Problem statement

AD is the most common form of dementia, and it possibly accounted for 50-75% of all cases of dementia, with higher occurrence rates in the older age groups (Braak & Tredici, 2012; Duthey, 2013). As life expectancy increases, the frequency of AD is expected to double by 2030 and triple by 2050, but neither the healthcare nor the financial systems globally are prepared to adequately address this magnitude of challenge (Duthey, 2013). The total global cost of dementia including AD in 2018 is US$1 trillion, and this figure will rise to US$ 2 trillion by 2030 if the trend continued (Patterson, 2018). According to the report made by Alzheimer's disease International (ADI) which Malaysia is a member country, the prevalence of dementia in Malaysia was 0.063% in 2005, with an annual incidence rate of 0.020%. It was also projected in the report that the figure would rise to 0.125% in 2020 and 0.454% in 2050 (Larson et al., 2006). Malaysia, like its counterpart countries in the Asia Pacific region, may not be well prepared to provide quality health care services for people with dementia including AD and their caregivers (WHO, 2006).

Although AD was first described more than 100 years ago, it was only after 70 years that it was recognised as the common cause of dementia, as well as a major cause of death (Katzman, 1976). Since then, AD became a significant area of research, thereby revealing much about the disease. However much more have yet to be discovered about the precise aetiology of AD, and why its progress varies among different individuals, as well as how it could be prevented, stopped or slowed (Gaugler et al., 2016).

In AD, the loss of cholinergic neurons and its subsequent decrease in cholinergic neurotransmission leads to behavioural and cognitive impairments. Low affinity N-methyl-D-aspartate (NMDA) antagonist and cholinesterase inhibitors (ChEIs) are the only classes of drugs approved by the United States Food and Drug Administration (USFDA) for symptomatic treatment of AD (Gaugler et al., 2016). Memantine, an NMDA glutamate receptor antagonist, acts via reduction of the glutamatergic neuronal excitotoxicity, while ChEIs, such as rivastimine, donepezil and galantamine, delay the hydrolysis of acetylcholine released into synaptic clefts, thus enhancing cholinergic transmission (Scheltens et al., 2016). Nevertheless, despite the high cost of new drug development, to date AD has no cure, although it has a high incidence rate and poses a huge economic burden. In addition, the commonly used drugs for AD have some harmful side effects, therefore it is necessary to seek for better alternative drugs for the prevention or treatment of AD.

1.3 Justification for the Study

Mouse models of ageing induced by combined administration of D-gal and AlCl3 have been used widely for several years for studying the mechanism of AD and for drugs screening (Cui et al., 2006; Luo et al., 2009; Wei et al., 2017). The use of D-gal/or AlCl3 on mice resulted in to old age/AD-like symptoms such as, oxidative stress, increased acetylcholinesterase (AChE) activities, decreased levels of ACh, high

BACE-1 expression and increased expression of Aβ associated molecules, which resulted to cognitive deficits (Jayant et al., 2016; Wei et al., 2017). The combination of D-gal and $AlCl_3$ for the construction of AD-like pathologies and cognitive impairments in mice have been optimised by previous works (Luo et al., 2009; Xiao et al., 2011). However, the long duration for the induction, the level of invasiveness and the use of mice have raised some concerns, besides mice being very fragile and too small for measurements of some AD-like physiological parameters. Therefore, there is a need for the combined administration of D-gal and $AlCl_3$ to optimize a rat model of AD for better understanding of AD-like pathologies and for drug screening purposes.

The traditional use of CA for centuries in the treatment of leprosy, skin diseases, wound healing and enhancement of memory in Ayurveda medicine, Chinese traditional medicine and African system of medicine has long been documented as reviewed by Chiroma et al., 2017. AD is characterised by two pathological hallmarks; the presence of abnormal tau protein in form of neurofibrillary tangles and deposits of Aβ senile plaques (SP) (Firuzi & Praticò, 2006). Further, oxidative stress and cholinergic dysfunction could also play a significant role in the pathogenesis and progression of AD (Santos et al., 2012). Asiaticoside, one of the triterpenoid components found in CA, reverses cognitive deficit in diabetic encephalopathy rats via anti-oxidative activity and modulation of the PI3K/AKt/NF-$_K$B pathway (Yin et al., 2015), while CA extract stimulates dendritic arborisation via activation of ERK1/2 and AKT pathway in neuroblastoma cells (Xu et al., 2008). Additionally, CA have been reported to have antioxidant, anti-apoptotic and anticholinesterase activities in aluminium (Al), arsenic, streptozotocin or D-gal induced rats (Gupta & Flora, 2006; Kumar et al., 2011; Amjad, 2015; Veerendra & Gupta, 2003) respectively. Notwithstanding, there is as yet no evidence for activity and mechanism of action of CA for preventing combined D-galactose (D-gal) and aluminium chloride ($AlCl_3$) induced neurotoxicity and cognitive deficits in AD-like rats model. This research has been conceptualised based on the possible attenuation of AD-like symptoms by extract of CA through amelioration of cognitive impairments by modulating cholinergic and oxidative stress pathways. The study further explores the potential use of CA in ameliorating AD-like changes through the inhibition of hyperphosphorylation of tau protein and apoptosis via the blockage of intrinsic mitochondria-mediated apoptosis pathway. Finally, the protective effects of CA on morphological alterations in the brains of AD-like rats were also explored. An overview of the thesis chapters is presented in figure 1.1.

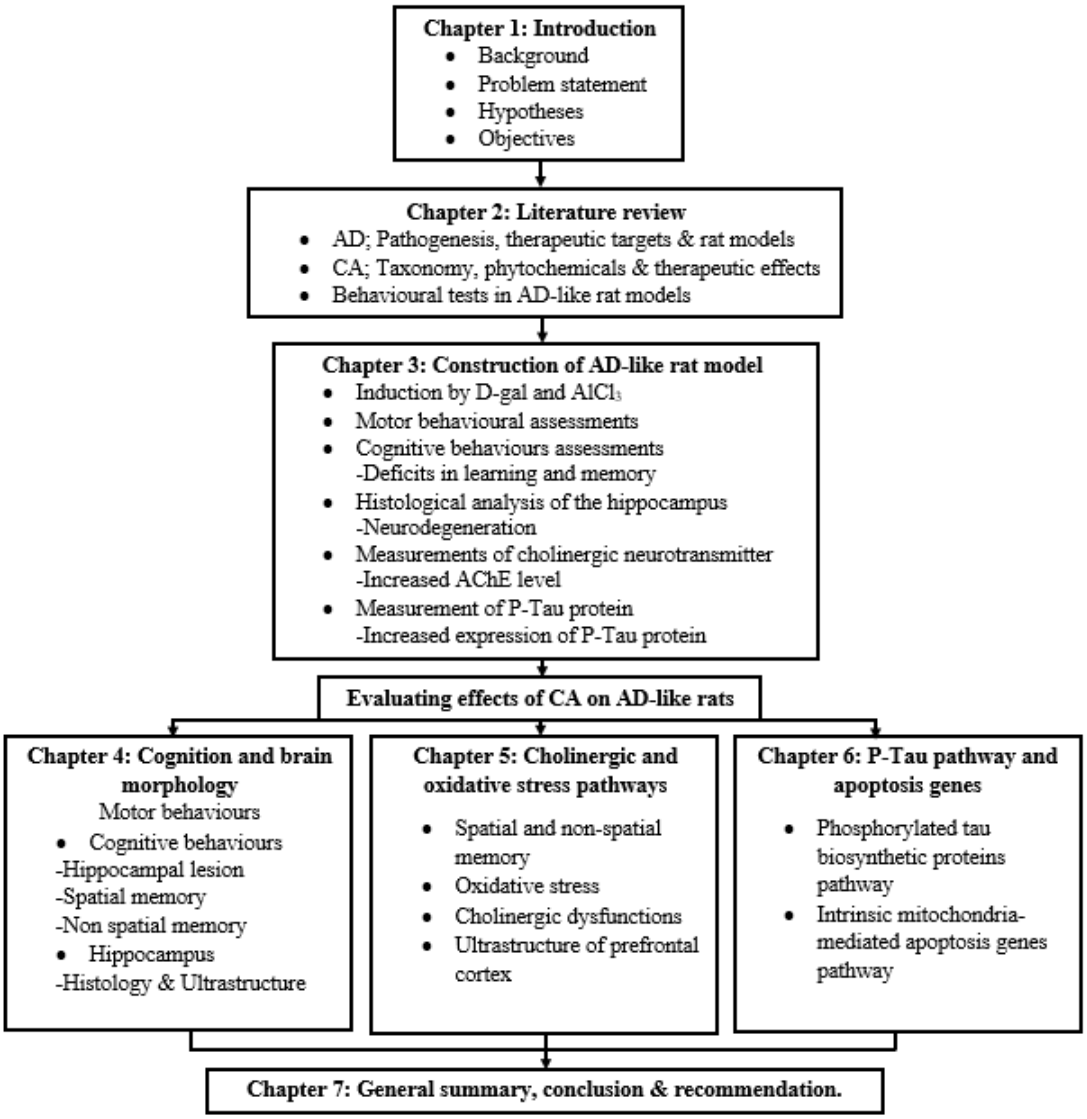

Figure 1.1 : Organisation of the thesis chapters. AD-Alzheimer's disease; $AlCl_3$-Aluminium chloride; CA-*Centella asiatica*; D-gal- D-galactose; P-Tau protein-Phosphorylated tau protein, AChE- Acetylcholinesterase

1.4 Hypothesis

- CA prevents D-gal and $AlCl_3$ induced neurotoxicity and cognitive impairment in rats
- CA increases the expression of PP2A and decreases the expression of GSK-3β proteins in the hippocampus of D-gal and $AlCl_3$ induced rats.

1.5 Objectives of the Study

1.5.1 General Objective

The objective of this study is to investigate the neuroprotective potentials of CA extract in D-gal and $AlCl_3$ induced toxicity and cognitive deficits in rats.

1.5.2 Specific Objectives

i. To produce and to confirm D-gal and $AlCl_3$ induced rat models of neurotoxicity and cognitive impairment.
ii. To evaluate the cognitive enhancing effects of CA on D-gal and $AlCl_3$ induced rats.
iii. To determine the protective effects of CA on structural changes in the brains of D-galactose and $AlCl_3$ induced rats.
iv. To evaluate the protective effects of CA on selected biochemical indices in the brains of D-gal and $AlCl_3$ induced rats.

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BIODATA OF STUDENT

Musa Samaila Chiroma is a Nigerian native of Borno state from the Askira/Uba local government area. He attended Askira Low-cost Primary School in Askira, where he obtained his First School Leaving Certificate in the year 1991. He then proceeded to the Government College Maiduguri in Maiduguri for his post primary education where he completed his Senior Secondary Certificate Examination (SSCE) in 1997. Musa gained admission in to 1 year Remedial Science Program of the University of Maiduguri in 1999, and after passing the stipulated courses he was admitted to B. Sc. Human Anatomy in the same university. He graduated in 2005 with second class (upper division) B.Sc. in Human Anatomy. In 2006, Musa answered his country's call by signing up to the one year compulsory National Youth Service Corps (NYSC), where he served in the city of Idanre of Ondo state. Besides being dedicated to his primary assignments in the Medical Laboratory where he was serving, Musa also did community development service at a secondary school in his host community. Hence, he was given an honorary award by the Ondo state NYSC headquarters for his selfless services to his nation. Musa was later employed by the University of Maiduguri in Nigeria, as a graduate assistant in the Department of Human Anatomy since 2013. He obtained his M.Sc. in Human Anatomy in 2015 from the University of Maiduguri in Nigeria, and enrolled for his PhD in Human Anatomy at Universiti Putra Malaysia (UPM). During the course of his PhD, Musa participated in the competitive three minutes thesis (3MT) competition at UPM and won first position in 2018. Musa is currently employed as a lecturer at the University of Maiduguri in Nigeria. He is happily married to one wife and has three children all boys.

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Conference Presentations

Musa S Chiroma, Mohamad A. Mohd Moklas, Mahamad T. Hidayat Baharuldin, Che Norma M. Taib, Zulkhairi Amom and Saravanan Jagadeesan, Protective effect of *Centella asiatica* against D-galactose and aluminium chloride induced rats: Behavioural and ultra-structural approaches. "International conference on drug discovery and translational medicine 2018 (ICDDTM '18)". Everly Putrajaya, Malaysia. (**Oral presentation**).

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Awards

1. **Putra grant 9535400** "Tawaran geran Universiti Putra Malaysia tahun 2017" (**RM 20,000.00)**.
2. **Second position** in PhD category, UPM Faculty of Medicine and Health Sciences "Three Minutes Thesis (3MT) competition 2017".
3. **First position** in PhD category, UPM Faculty of Medicine and Health Sciences "Three Minutes Thesis (3MT) competition 2018".
4. **Overall best,** UPM Three Minutes Thesis (3MT) competition 2018.
5. **Second best** oral presenter, at "International conference of drug discovery and translational medicine 2018 (ICDDTM '18)".

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