UNIVERSITI PUTRA MALAYSIA

NEUROTHERAPEUTIC POTENTIAL OF SYNTHETIC CANNABINOID RECEPTOR AGONIST, WIN55,212-2 ON ALUMINIUM CHLORIDE AND D-GALACTOSE INDUCED COGNITIVE IMPAIRMENTS IN MALE WISTAR RATS

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By

MAHDI ONESIMUS

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

September 2021

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DEDICATION

This work is dedicated to God almighty, my lovely wife; Mrs Esther Onesimus Mahdi and children: O'Brien Yele Onesimus and Olivia-Minki Onesimus

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

NEUROTHERAPEUTIC POTENTIAL OF SYNTHETIC CANNABINOID RECEPTOR AGONIST, WIN55,212-2 ON ALUMINIUM CHLORIDE AND D-GALACTOSE INDUCED COGNITIVE IMPAIRMENTS IN MALE WISTAR RATS

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September 2021

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

Cognitive impairments and neurotransmission dysfunction have been linked to old age diseases including Alzheimer's disease (AD). Aluminium has been reported to act as a neurotoxic metal, whereas D-galactose (D-gal) has been established to be a senescence agent. Donepezil is in a class of medications called cholinesterase inhibitors. It improves mental function such as memory and attention by increasing the amount of a certain naturally occurring substance in the brain. WIN55,212-2 (WIN), is a potent cannabinoid agonist which has been reported to restore neurogenesis in aged-rats in addition to its neuroprotective roles on oligodendrocytes as well as thermoregulation related to the activation of central CB1 receptors. However, there is paucity of information with regards to therapeutic potentials of WIN on Aluminium chloride ($AlCl_3$) and D-gal induced rat model. Hence, the present study established AD-like rat model of neurotoxicity and cognitive impairment induced by $AlCl_3$ and D-gal in order to explore the therapeutic potentials of WIN for the treatment AD-like symptoms in rats. Healthy male albino Wistar rats weighing between 200 g - 250 g were injected with D-gal 60 mg/kg intra peritoneally (i.p), while $AlCl_3$ (200 mg/kg) was orally administered once daily for 10 consecutive weeks. For behavioural assessments: elevated plus maze (EPM), open field test (OFT), Morris water maze (MWM), Novel object recognition (NOR) and T-maze tests were performed. Further, histopathological examinations of the hippocampi and the prefrontal cortices were also carried-out besides, measurements of acetylcholine (ACh) and amyloid beta of the rat's brains. Subsequently, commencing from week 8 of the experiment, rats were co-administered with WIN (0.5, 1 and 2 mg/kg) and donepezil 1 mg/kg until week 11. Behavioural assessments of the rats and morphological analysis (Nissl's staining and light microscopy) of their brains were carried out. Further, oxidative stress biomarkers: Malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) were assessed. The results revealed that rats treated with $AlCl_3$ 200 mg/kg/day and D-gal 60 mg/kg/day showed cognitive impairments in both spatial and non-spatial learning and memory tests, which is also

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associated with marked neuronal loss ($p < 0.05$), increased oxidative stress ($p < 0.05$) and decreased ACh level ($p < 0.05$) in their brains. Additionally, significant decrease in the expressions of glial fibrillary protein (GFAP) ($p < 0.05$), Nestin ($p < 0.05$) and high levels of amyloid beta 42 (Aβ42) in their brains were also evident. However, administration of WIN (0.5 mg/kg/day, 1 mg/kg/day and 2 mg/kg/day) doses reversed the cognitive impairments and the associated AD-like pathologies. As there was increases in the levels of ACh SOD and GSH, while a significant decrease in the levels of MDA and Aβ42 were also observed besides attenuation of aberrant cytoarchitecture of the rat's hippocampus and prefrontal cortex. Hence, exhibiting therapeutic effects which could be attributed to WIN's ability to reduce oxidative stress and stop neurodegeneration thereby enhancing cognitive ability. All these findings provide possible scientific evidence to support the exploration of cannabinoid agonist, WIN and other cannabinoids as safe and effective compounds to consider in the treatment of AD related cognitive deficits. Overall, the results of the WIN-treated rats were comparable with the Donepezil group of rats.

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

POTENSI TERAPEUTIK NEURO AGONIS RESEPTOR KANABINOID, WIN55,212-2 TERHADAP PERENCATAN FUNGSI KOGNITIF YANG DIARUH OLEH ALUMINIUM KLORIDA DAN D-GALAKTOSA PADA TIKUS JANTAN WISTAR

Oeh

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Pengerusi : Profesor Madya Mohamad Aris Mohd Moklas, PhD
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Penyakit dikalangan orang tua, seperti penyakit Alzheimer (AD) sering dikaitkan dengan perencatan fungsi kognitif dan kegagalan neuropenghantaran. Logam aluminium telah dilaporkan sebagai bahan yang bersifat neurotoksik, manakala D-galaktosa (D-gal) merupakaan ejen penuaan. Donepezil merupakan ubatan yang dikelaskan sebagai perencat kolinesterase. Ia meningkatkan fungsi mental seperti memori dan kawalan perhatian dengan meningkatkan aras bahan semula jadi yang tertentu di dalam otak. WIN55,212-2 (WIN) merupakan agonis kanabinoid yang poten dan ia dilaporkan mampu untuk memulihkan sebagahagian neurogenesis pada tikus tua, memberikan perlindungan neuro terhadap oligodendrosit, dan terlibat dalam termoregulasi melalui pengaktifan reseptor pusat CB1. Walau bagaimanapun, maklumat mengenai potensi terapeutik WIN terhadap model tikus yang diaruh oleh Aluminium klorida ($AlCl_3$) dan D-gal adalah terhad. Oleh yang demikian, kajian ini dirangka untuk meneroka potensi terapeutik WIN untuk merawat simptom-simptom AD dengan menghasilkan model tikus seperti AD yang merangkumi neurotoksik dan perencatan fungsi kognitif yang di aruh oleh $AlCl_3$ dan D-gal. Kajian menggunakan tikus jantan Wistar albino yang sihat dan mempunyai berat badan 200 g hingga 250 g. Tikus diaruh setiap hari melalui suntikan 60 mg/kg D-gal secara intraperitoneum (i.p) dan pemberian $AlCl_3$ (200 mg/kg) adalah secara oral, berturutan selama 10 minggu. Untuk penilaian tingkah laku, protokol ujian yang dilakukan ialah ujian pagar sesat ternaik (EPM), ujian ruang terbuka (OFT), ujian pagar sesat air Morris (MWM), ujian pengecaman objek novel (NOR) dan ujian pagar sesat T. Kajian yang dilakukan turut meliputi aspek-aspek berikut; pengukuran aras asetilkolina (ACh) dan beta amiloid pada otak tikus, serta pemeriksaan perubahan histopatologikal pada hipokampus dan korteks prefrontal tikus. Bermula pada minggu ke 8 proses aruhan, tikus akan menerima suntikan WIN (0.5, 1 dan 2 mg/kg) dan donepezil 1 mg/kg sehingga minggu ke 11. Penilaian tingkah laku dan analisis morfologi (pewarnaan Nissl dan mikorskop cahaya) otak tikus dilakukan selepas miggu ke 11. Sebagai tambahan, kajian turut menganalisis aras biopenanda untuk stres oksidatif

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seperti malondialdehid (MDA), superoksida dismutase (SOD) dan glutation (GSH). Turut dianalisis ialah beta amiloid (Aβ) dan proten sintetiknya, serta biopenanda apoptosis.

Hasil kajian menunjukkan tikus yang diaruh dengan $AlCl_3$ 200 mg/kg/hari dan D-gal 60 mg/kg/hari mengalami kemerosotan fungsian kognitif spatial dan bukan spatial melalui ujian pembelajaran dan memori, dan ia berkaitan dengan kemerosatan neuron yang signifikan ($p < 0.05$), peningkatan aras stres oksidatif ($p < 0.05$) dan menurunan aras ACh ($p < 0.05$) di dalam tisu otak. Sebagai tambahan, terdapat menurunan aras yang signifikan pada ekspresi protein fibril glial (GFAP) ($p < 0.05$) dan Nestin ($p < 0.05$), serta aras beta amiloid 42 (Aβ42) yang tinggi di dalam tisu otak. Secara amnya, profil biokimia tikus yang dirawat oleh WIN adalah normal. Walau bagaimanapun, rawatan pelbagai dos WIN (0.5 mg/kg/hari, 1 mg/kg/hari dan 2 mg/kg/hari) dapat memulihkan kemerosotan fungsian kognitif seperti patologi AD. Terdapat meningkatan aras yang signifikan untuk bacaan ACh, SOD, dan GSH. Manakala penurunan aras yang signifikan direkod pada bacaan MDA dan Aβ42, di samping pemerosotan sitoarkitektur yang aberan pada hipokampus dan korteks prefrontal. Oleh yang demikian, WIN menunjukkan kesan terapeutik dengan meningkatkan kebolehan fungsian kognitif melalui keupayaannya untuk merencat stres oksidatif, serta menghalang neurodegenerasi dan apoptosis. Kesemua hasil kajian memberikan bukti saintifik dimana eksplorasi agonis kanabinoid WIN atau kanabinoid agonis yang lain sebagai potensi kompaun yang selamat dan efektif untuk merawat AD yang berkaitan dengan kemerosotan fungsian kognitif. Secara keseluruhan, dapatan kajian mendapati tikus yang dirawat oleh WIN adalah standing dengan tikus yang menerima rawatan Donepezil.

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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:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
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LIST OF ABBREVIATIONS

Δ	Delta
2-AG	2-arachidonoylglycerol
5-HT	serotonin
Ach	Acetylcholine
AChE	ACh-hydrolysing enzyme
AChEI	Acetylcholinesterase inhibitors
AChRs	acetylcholine receptors
AD	Alzheimer's disease
ADI	Alzheimer's Disease International
AGEs	advanced glycation end products
AID	Aged-Induced Dementia
AIF	apoptosis-inducing factor
Al	Aluminium
ALCL3	Aluminium chloride
ALS	Amyotrophic lateral sclerosis
ANA	Anandamide
ANOVA	Analysis of variance
Apaf-1	Apoptotic protease-activating factor 1
apoE	apolipoprotein E
ApoE2	Apolipoprotein E2
ApoE3	Apolipoprotein E3
ApoE4	apolipoprotein-E4
APP	amyloid precursor protein
ATP	Adenosine triphosphate
Aβ	Beta amyloid

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Aβ40	Beta amyloid 40
Aβ42	Beta amyloid 42
AβPP	amyloid beta precursor protein
BBB	Blood brain barrier
BCA	Bicinchoninic acid assay
BCCAO	Common carotid arteries occlusion
CA1	Cornu ammonis 1
CA2	Cornu ammonis 2
CA3	Cornu ammonis 3
CA4	Cornu ammonis 4
CB1	cannabinoid receptor 1
CB2	cannabinoid receptor 2
ChEIs	Cholinesterase inhibitors
ChEIs	Cholinesterase inhibitors
CNS	Central nervous system
COX	cytochrome c oxidase
COX2	Cyclooxygenase 2
CRP	C- reactive protein
CS	Cannabis sativa
CT	Computerized tomography
CVD	Cardiovascular disease
cyt-c	Cytochrome c
DG	Dentate gyrus
D-gal	D-galactose
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid

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DW	Distilled water
EC	Endocannabinoid system
ELISA	Enzyme-linked immunosorbent assay
EPM	EPM
ETC	electron transport chain
FAD	familial Alzheimer's Disease
FDA	Food and drug administration
GABA	γ-aminobutyric acid
GFAP	Glial fibrillary protein
Glu	glutamate
GP	Group
GPCRs	G-Protein Couple Receptors
GSSG	Oxidised Glutathione
GSH	Glutathione
H & E	Haematoxylin and Eosin.
H0-	Hydroxyl
H2O2	Hydrogen peroxide
HRP	Horseradish peroxidase
i.p	Intraperitoneal
IACUC	Institutional Animal Care and Use Committee
IL-1	Interleukin 1
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
iNOS	Inducible nitrate oxide synthase
IRs	Insulin receptors
kDa	Kilodalton

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Kg	Kilogram
LPS	Lipopolysaccharide
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinases
MAPT	microtubule associated protein tau
MDA	Malondialdehyde
MMSE	Mini-Mental State Examination
MPT	Prompt mitochondrial permeability transition
MRI	magnetic resonance imaging
MWM	Morris water maze
NA	Not applicable
NF-Kb	Nuclear factor kappa-light-chain-enhancer
NFTs	neurofibrillary tangles
NMDA	N-methyl-D-aspartate
NMDAr	N-methyl-D-aspartate receptor
NO	Nitric oxide
NOR	Novel object recognition
NS	Normal saline
NSCs	Neural stem cells
OFT	Open Field Test
OH	Hydroxyl radical
OH-	hydroxyl anion
ONOO-	Peroxynitrite
p.o	Per oral
PBS	Phosphate buffered saline
PET	positron emission tomography

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PHF	Paired helical filament
PI3K/AKT	Phosphoinositide 3-kinase
PPARγ	Peroxisome proliferator-activated receptor gamma
PSEN1	Presenilin1
PSEN2	Presenilin2
P-Tau	Phosphorylated tau
RIPA	Radioimmunoprecipitatation assay
ROS	Reactive oxygen species
SAD	Sporadic Alzheimer's disease
SAMP	Senescence Accelerated Mice Model
SEM	Standard error of mean
SOD	Superoxide dismutase
SP	senile plaques
TBI	traumatic brain injury
T-GSH	Total glutathione
THC	Tetrahydrocannabinol
TNF-α	tumor necrosis factor alpha
USFDA	United States Food and Drug Administration
VGCC	Voltage-gated ion channel
WIN	WIN55,212-2
αAPPs	Alpha amyloid precursor proteins
Γ	Gamma

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CHAPTER 1

INTRODUCTION

1.1 Background

Alzheimer's Disease (AD) is a progressive, multifactorial and incurable age-related neurodegenerative disease which was first described by Alois Alzheimer, a German Clinical Psychiatrist and neuroanatomist in 1906, hence it was named after him (Hippius, 1998; Zakaria et al., 2017). AD is the most frequent type of dementia and accounts for about two thirds of all dementia cases globally among people aged 65 years and above (Kumar et al., 2018). Clinically, AD is characterised by progressive impairment of cognitive functions which includes memory, attention, comprehension, reasoning, language and judgement (Kumar et al., 2018; Tarawneh & Holtzman, 2012).

There are two types of AD, familial (early onset) and sporadic (late onset). The sporadic type is the most prevalent form of AD often diagnosed and its aetiology remains elusive (Flamier et al., 2018). Early onset AD is a condition characterized by dementia in individuals less than 65 years of age with a positive family history which accounts for about 5% of AD cases and includes at least 230 mutations in three genes coded and implicated in AD (Lleó et al., 2002). The three genes are amyloid beta precursor protein (AβPP) gene on chromosome 21, Presenilin1 (PSEN1) gene on chromosome 14 and Presenilin2 (PSEN2) gene on chromosome 1. These genes were linked to the Aβ peptide located in the senile plaque (SP) in the brain of patients with AD (Kok, 2011). The general consensus is that, most mutations of the three genes (AβPP, PSEN1 and PSEN2) cause excessive accumulation of Aβ, leading to formation of toxic forms of Aβ peptide, which in turn aggregate into SP and purportedly disrupt neuronal messaging finally causing death of the neurons (Zhang et al, 2001). Late onset AD is the most rampant form of AD cases being diagnosed and has no known aetiology (Flamier et al., 2018). It usually occurs in patients over 65 years and thus refer as late onset AD. In contract to the familial form of AD which is hereditary, research has uncovered that apolipoprotein E (apoE) gene on chromosome 19 which codes for a protein that aids to transport cholesterol in the blood stream plays a role in increasing the risk of developing sporadic AD (Poirier, 2003). While there are quite a lot of alleles of apoE, only three occur most frequently, viz. apoE2 (E2), apoE3 (E3) and apoE4 (E4). People inherit one apoE allele from each parent. Inheritance of one or two copies of allele E4 increases the risk of AD while E2 reduces the risk of developing AD (Di Battista et al, 2016).

According to recent statistics (2019), about 50 million people are living with AD, making this condition the most frequent major neurocognitive disorder globally (Guo et al., 2020; International, 2018; Prince et al., 2016). Further, AD is one of the sixth top leading causes of death in the US and the fifth leading cause of the death among elderly people aged 65 years and above (Alzheimer's & Dementia, 2015). The pathologic hallmarks of AD are Amyloid beta (Aβ) plaques formed by the accumulation of extracellular deposits called senile plaques (SP), neurofibrillary tangles (NFTs) formed by the

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hyperphosphorylation of tau protein, gliosis, loss of neurons (Iqbal et al., 2016; Iqbal & Grundke-Iqbal, 2002; Petrella et al., 2019; Terry et al., 1991). Other hallmarks are cerebrovascular amyloidosis, inflammation and significant synaptic changes (Dansokho & Heneka, 2018; Katsumoto et al., 2018; Tönnies & Trushina, 2017). Although the aetiology of these hallmarks has remained elusive but emerging evidence have revealed that deficit in cholinergic neurotransmission are also implicated in AD pathogenesis (Sohre & Moosmann, 2018). These neurotransmission deficits are elucidated by irregular release of neurotransmitters in the brain such as acetylcholine (ACh), γ-aminobutyric acid (GABA), glutamate (Glu) and serotonin (5-HT) (Prakash et al, 2015). Furthermore, the disease can also be categorised into early-onset and late-onset on the basis of age in which it manifests. The early-onset AD is evident between ages of 30 to 60 and is responsible for about 1-6% of cases identified whereas the late onset form of AD appears beyond age 60 responsible for over 90% of all occurrences (Anand et al., 2014).

Cannabis is one of the oldest crops cultivated by mankind and now grown all over the world (Hartsel et al., 2016). Documentary evidence dating back thousands of years suggest that Cannabis has long been harnessed as a source of food or oil and medicine in Chinese traditional medicine to treat many illnesses (Brand & Zhao, 2017). Although cannabis still stands a banned substance globally, in recent times the scientific community along other group of people have been pursuing the legitimisation of this plant due to its huge health benefits (Bostwick, 2012). The plant contains hundreds of different chemical compounds that gives moderate reactions, sense of relief and huge health benefits for people affected by wide range of illnesses through its contact with the endocannabinoid system in the humans (Aguilar et al., 2018). Tetrahydrocannabinol (THC), is the psychoactive component and the most investigated out of the over 100 compounds unique to the cannabis plant, that are called cannabinoids. However, different properties for other cannabinoids are continually being uncovered; for instance, terpenes and flavonoids have been identified to demonstrate therapeutic properties. Few studies have reported that THC can stimulate the nervous system and induce neurogenesis (Suliman et al., 2018). THC is particularly known to ameliorate neuroinflammation and has neuroprotective properties.

WIN55,212-2 (WIN), is a potent synthetic aminoalkylindole cannabinoid which is gaining momentum to be used as a tool in cannabinoid research as it has been shown to produce full spectrum of in vivo effects via endocannabinoid system observed in THC and other cannabinoids (Lauckner et al., 2005). Administration of WIN has been shown to restore neurogenesis in the hippocampus of aged rats although not in a pathological setting. These synthetic cannabinoid agonists, WIN has been reported to exert its action through the endocannabinoid system (EC). The EC is a neuromodulatory signaling complex that encompasses cannabinoid receptors, their endogenous ligands, and proteins implicated in the formation, transport and degradation of such ligands (Lu & MacKie, 2016). Unravelling the presence and distribution of the cannabinoid receptor 1 (CB1) in the rodent and human central nervous system has implicated this signaling system in several facets of the development process (Erdozain et al., 2015; Harkany et al., 2008; Macías-Triana et al., 2020; Yi et al., 2016).

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Thus, suggesting that cannabinoid receptor stimulation therapy may be considered to have clinical benefit for humans with age-related memory impairment (Marchalant et al., 2009; Wang, 2019). Further, numerous findings have charted the localization of cannabinoid receptors precisely in tissues and at a subcellular level, and these have been crucial to our understanding of the effects of cannabinoids in disease. CB1 receptors are expressed in both the central nervous system and peripheral nervous system. They are known to stimulate and mobilise receptors within the cell. Significantly, CB1 receptors are universal in the affective memory neurocircuitry, which comprises the hippocampus, amygdala, and prefrontal cortex (Gouveia et al., 2019; Piomelli, 2003).

Due to their various neuromodulatory functions, the role of cannabinoids in neurogenesis has been of particular interest in recent years (Jiang et al., 2005). Cannabinoid receptors has been shown to modulate adult neurogenesis through acting at specific neurogenic phases (Riksson et al., 1998). Significantly, CB1 or cannabinoid receptor 2 (CB2) receptors by selective agonists has been shown to play a role in cell proliferation, neuronal differentiation and maturation (De Petrocellis, Ligresti, 2011; Martín-Moreno et al., 2011; Steel et al., 2014). In NSCs and their neuronal progenies, CB1 and CB2 receptors' expression varies during the various stages of neuronal differentiation, with CB1 increasing with neural maturation and CB2 becoming more abundant in less dedicated cells (Niaz et al., 2017). They are the most abundant G-Protein Couple Receptors (GPCRs) in the brain, with high expression levels in the basal ganglia and moderately expressed in the hippocampus, cerebellum and neocortex (Glass & Felder, 1997; Herkenham et al., 1990). At the subcellular level, CB1 has been reported to expressed in pre-synaptic terminals, and is found at expressively higher levels on GABAergic than glutamatergic neurons in various brain regions (Katona et al., 2001; Katona et al., 1999; Puighermanal et al., 2009).

1.2 Statement of Research Problem

AD has high prevalence of 60-80% of all dementia and is accompanied with huge economic burden on the society. Moreover, the known medications for the treatment of AD are limited in number and is still no cure for this age-related neurodegenerative disease. Its features are disruption of several brain functions, including learning capacity, thinking, memory, orientation, calculation, comprehension, language and judgement. Although the discovery of AD is over a century now, only about 70 years later before it was understood as the frequent cause of dementia as well as a leading cause of death among many older people (Katzman, 1976). Since then, Alzheimer's disease has attracted several researchers to explore the brain and a lot has been unravelled about the disease. However, there are countless issues to be unravelled regarding its exact cause, why its advancement differs from person to person and how it can be prevented, stopped or delayed (Gaugler et al., 2016).

WIN together with JWH and HU-210 are accountable for averting the inflammation induced by Amyloid beta protein implicated in Alzheimer's disease, apart from preventing cognitive impairment and loss of neuronal markers (Prenderville et al., 2015). In addition, WIN could prevent cognitive impairment and loss of neuronal circuitry.

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Further, cannabinoids reduce neurotoxicity related to microglial activation in rat models of cognitive impairments both in vivo and in vitro (Martín-Moreno et al., 2011). Cannabinoids, the active compounds of marijuana and their likes, exert a variety of central and peripheral effects by activating specific cannabinoid receptors. To date, CB1 and CB2 receptors are the two cannabinoids receptors that have been well characterized (Howlett, 2002; Piomelli, 2003). CB1 receptors are highly expressed and localised predominantly in the nervous system (Herkenham et al., 1990; Zou & Kumar, 2018), in that they mediate cannabinoid psychoactivity and are expressed by all types of neural cells. In addition to being found in neurons, CB1 receptors exist in astrocytes (Bouaboula et al., 1995; Zou & Kumar, 2018). In the cortex and in the hippocampus, GABAergic neurons highly expressed CB1 receptors cells, while to a lesser extent, glutamatergic principal neurons express CB1 receptors (Marsicano & Lutz, 1999). In contrast, CB2 receptors are solely expressed in the cells and organs of the immune system and is considered to mediate cannabinoid induced immune modulation (Galiègue et al., 1995; Ramirez et al, 2005). The involvement and role of CB2 receptors in the central nervous system have yet to be uncovered and still up to debate for some reasons. Although, one researcher has affirmed that CB2 receptor is not entirely absent from the brain, since it is relatively expressed in microglia (Klegeris et al., 2003).

1.3 Justification for the study

The nonselective CB agonist, WIN, also plays a significant role in thermoregulation related to the activation of central CB1 receptors. Furthermore, there are a number of findings pointing the involvement of WIN in the restoration of neuronal loss. However, there is paucity of reports regarding its neuro-therapeutic activity and mechanism of action in prevention of neurotoxicity with respect to AD-like symptoms. Further, no available studies have demonstrated the neurotherapeutic potential of WIN activity in preventing neurotoxicity and cognitive deficits induced by the co-administration $AlCl_3$ and D-gal in AD-like rat model. This work has been conceived based on the possible attenuation of AD-like symptoms by WIN via amelioration of cognitive impairments by modulating cholinergic and oxidative stress pathways. The research further explores the potential of WIN in ameliorating AD-like changes through the inhibition of Aβ42 accretion in the hippocampus. Finally, the neurotherapeutic potential of WIN on morphological alterations in the brains of AD-like rats were also explored through histological studies. An overview of the thesis chapters is presented in **Figure 1.1**

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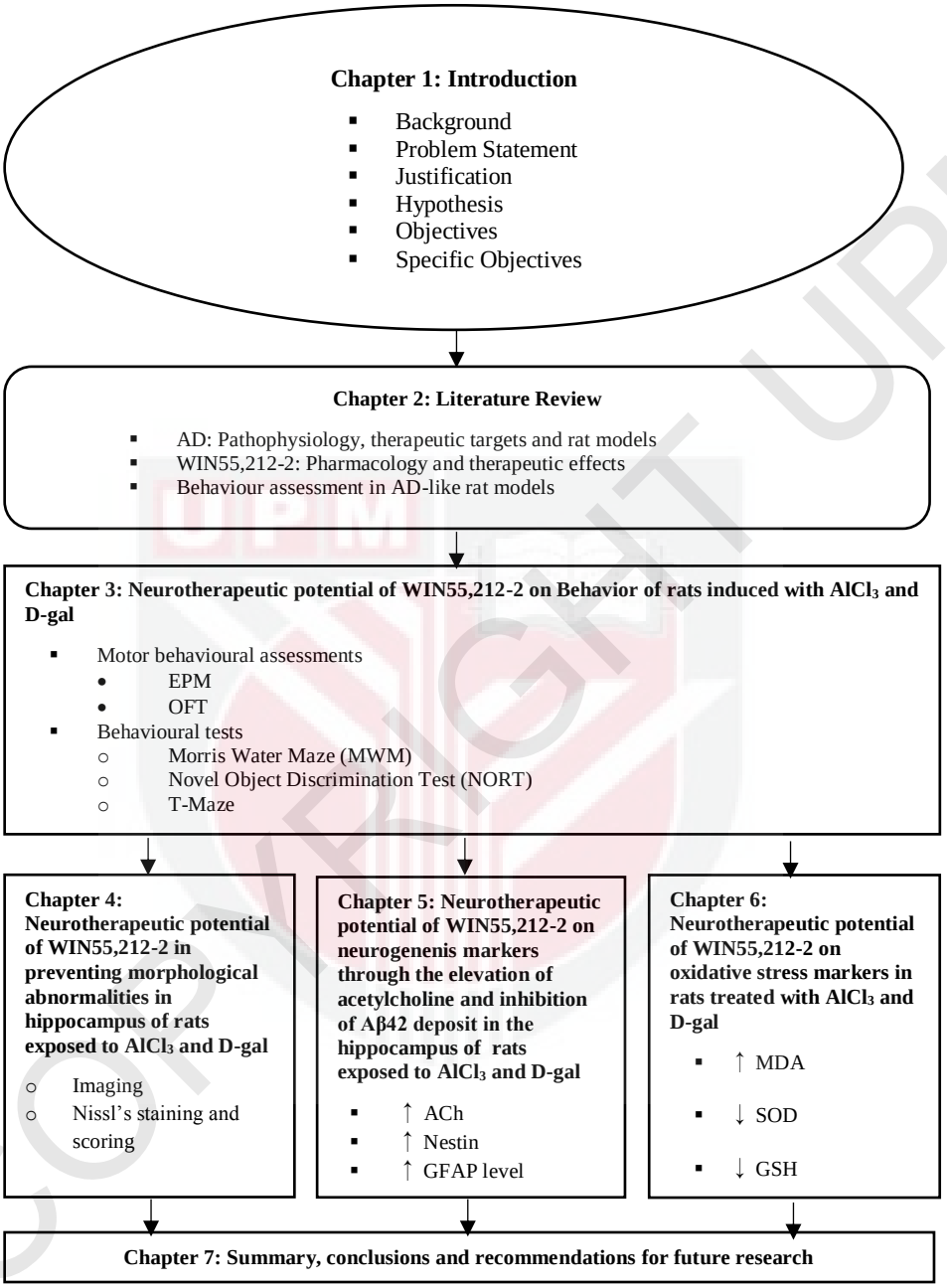

Figure 1.1 : Organisation of thesis chapters. This is the thesis design and a brief schematic presentation of how the experiment was conducted and actualised. AD – Alzheimer's Disease, $AlCl_3$ – Aluminium Chloride, D-gal – D-galactose, ACh – Acetylcholine, Aβ42 – Beta Amyloid 42, GFAP – Glial fibrillary acid protein, MDA – Malondialdehyde, SOD – superoxide dismutase, GSH - glutathione

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1.4 Hypothesis

HO: Treating rats exposed to $AlCl_3$ and D-galactose with WIN55,212-2 would ameliorate cognitive impairments.

HA: Treating rats exposed to $AlCl_3$ and D-galactose (D-gal) with WIN 55,212-2 would not ameliorate cognitive impairments.

1.5 Objective of the Study

1.5.1 General Objective

To investigate the neurotherapeutic potential of WIN55,212-2 on $AlCl_3$ and D-Gal induced neurotoxicity in rats.

1.5.2 Specific Objectives

1. To evaluate the neurotherapeutic potential of WIN55,212-2 on cognitive functions in rats after $AlCl_3$ and D-gal exposure.
2. To determine the neurotherapeutic potential of WIN55,212-2 on the histology of hippocampus in rats following $AlCl_3$ and D-gal treatment.
3. To evaluate the neurotherapeutic potential of WIN55,212-2 on neurogenesis markers through the elevation acetylcholine and the inhibition of Aβ42 in rats treated with $AlCl_3$ and D-gal.
4. To evaluate the neurotherapeutic potential of WIN55,212-2 on oxidative stress markers in rat exposed to $AlCl_3$ and D-gal.

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