EFFECTS OF ZERUMBONE ON ANXIETY, LEARNING AND MEMORY IN SCOPOLAMINE-INDUCED ANIMAL MODEL OF DEMENTIA

By

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Chairman : Associate Prof. Enoch Kumar Perimal, PhD
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Dementia is a general term to describe decline of mental ability associated with cognitive impairment, losing memory or other thinking skills that interfere with occupational functioning and usual social activities. The most common type of dementia is Alzheimer's disease (AD) which is a neurodegenerative disease related to cognitive and behavioural impairments. The major AD drugs are known as acetylcholinesterase inhibitors (AChEI) which are not acceptable in a wide range of patients due to resistance, adverse effect, and poor efficacy. Based on recent studies, herbal medicine such as zerumbone (2,6,9,9-tetramethyl-[2E,6E,10E]-cycloundeca-2,6,10-trien-1-one) which is a sesquiterpenoid compound, could be a new source for inhibition of AChE enzyme. Zerumbone was first isolated from the rhizomes oil of *Zingiber zerumbet Smith*, in 1956. It has the potential for treatment of cancers, leukemia and virus infection. In this study, scopolamine which is a muscarinic antagonist drug was used to induce some dementia-like behaviours in rats and the effect of zerumbone (1 and 10mg/kg) was investigated through some behavioural and biochemical experiments. All the results were expressed as mean ± standard error of mean (SEM) and analyzed using one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* analysis. $p<0.05$ was considered statistically significant. Behavioural assessments such as open field tests, elevated plus maze, and Morris water maze were performed to assess general locomotors activity, anxiety-like behaviours, and learning and memory processes respectively, in Sprague-Dawley rats pre-treated with scopolamine. Based on the results obtained, zerumbone 1 mg/kg significantly reduced total activity, stereotype, and total distance travelled in the open field arena. Moreover, zerumbone 1 and 10mg/kg, respectively showed high percent of time spent in open arms; and increased number and percent of entry to open arms, in the elevated plus maze. Also, in the Morris water maze, zerumbone 1 and 10mg/kg showed learning improvement by significant reduction in mean escape latency time. Interestingly, single administration of zerumbone (1 and 10mg/kg) reversed the hyperactivity, anxiety-like behaviour, and learning impairment effects of scopolamine to normal condition. Biochemical experiments have been done on the brain samples which were sectioned to three parts (prefrontal cortex, hippocampus, and cortex) and prepared for acetyl cholinesterase (ACHE) enzyme activity and choline acetyltransferase (ChAT) protein

expression. AChE enzyme activity is significantly reduced by zerumbone 1mg/kg in the hippocampus brain samples compared to all groups. On the other hand, lower dose of zerumbone reversed the effect of scopolamine by decreasing AChE enzyme activity. Western blotting was also used to determine ChAT protein expression among all groups and it was concluded that there isn't any significant differences between all groups and both dosage of zerumbone were not effective towards ChAT protein expression. In conclusion, zerumbone showed improvement in learning process while reduced hyperactivity, anxiety/depression, and AChE enzyme activity in scopolamine pre-treated rats. Thus, zerumbone could be a great candidate for treatment of dementia-like behaviour. Although, more research need to be done to find out its mechanism of action.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

KESAN ZERUMBON PADA ANXIETY, PEMBELAJARAN DAN MEMORY DALAM MODEL ANIMAL YANG DIPERLUKAN SCOPOLAMINE

Oleh

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Dementia adalah istilah umum untuk menggambarkan kemerosotan keupayaan mental yang berkaitan dengan kemerosotan kognitif, kehilangan ingatan atau kemahiran berfikir yang lain yang mengganggu aktiviti sosial yang berfungsi dan biasa. Jenis demensia yang paling biasa adalah penyakit Alzheimer (AD) yang merupakan penyakit neurodegenerative berkaitan dengan masalah kognitif dan tingkah laku. Ubat-ubatan utama AD dikenali sebagai perencat acetilkolinesterase (AChEI) yang tidak dapat diterima dalam pelbagai jenis pesakit akibat rintangan, kesan buruk, dan keberkesanan yang lemah. Berdasarkan kajian terkini, ubat herba seperti Zerumbone (2,6,9,9-tetramethyl- [2E, 6E, 10E] -cycloundeca-2,6,10-trien-1-one) yang merupakan sebatian sesquiterpenoid, boleh menjadi sumber baru untuk merencet enzim AChE. Zerumbone mula terpencil dari minyak rhizomes *Zingiber zerumbet* Smith, pada tahun 1956. Dalam kajian ini, scopolamine yang merupakan ubat antagonis muscarinik digunakan untuk menimbulkan beberapa kelakuan seperti demensia dalam tikus dan kesan zerumbon (1 dan 10mg / kg) disiasat melalui beberapa eksperimen tingkah laku dan biokimia. keputusan dinyatakan sebagai min ± kesilapan piawai bagi min (standard error mean, SEM) dan dianalisis dengan menggunakan analisa varians satu hala “one way analysis variance, ANOVA” diikuti dengan analisis post hoc Tukey. $p < 0.05$ dianggap signifikan secara statistik. Tinjauan kelakuan seperti “open field test”, “elevated plus maze”, dan “Morris water maze” dilakukan untuk menilai aktiviti lokomotif umum, tingkah laku seperti kecemasan, dan proses pembelajaran dan memori masing-masing, pada tikus Sprague-Dawley yang telah dirawat dengan skopolamin. Berdasarkan keputusan yang diperoleh, zerumbone 1 mg / kg mengurangkan jumlah aktiviti, stereotaip, dan jarak keseluruhan yang dijalani di arena lapangan terbuka. Lebih-lebih lagi, zerumbone 1 dan 10mg / kg, masing-masing menunjukkan peratus masa yang banyak digunakan dalam tangan terbuka; dan peningkatan bilangan dan peratus penyertaan untuk membuka senjata, dalam peningkatan ditambah labirin. Selain itu, dalam ujian “Morris water maze”, zerumbon 1 dan 10mg / kg menunjukkan peningkatan pembelajaran dengan pengurangan ketara dalam masa latensi melepaskan min. Menariknya, zerumbon tunggal (1 dan 10mg / kg) menganbalikom hiperaktif, kelakuan seperti kecemasan, dan kesan kemerosotan

pembelajaran scopolamine kepada keadaan normal. Eksperimen biokimia telah dilakukan ke atas sampel otak yang terbahagi kepada tiga bahagian (korteks prefrontal, hippocampus, dan korteks) dan disediakan untuk liputan protein enzim asetil kolinesterase (ACHE) dan choline acetiltransferase (ChAT). Aktiviti enzim AChE dikurangkan dengan ketara oleh zerumbone 1mg / kg dalam sampel otak hippocampus berbanding semua kumpulan. Sebaliknya, zerumbon denyutan yang lebih rendah membalikkan kesan scopolamine dengan mengurangkan aktiviti enzim AChE. Pembengkakan Barat juga digunakan untuk menentukan ungkapan protein ChAT di kalangan semua kumpulan dan disimpulkan bahawa tidak terdapat perbezaan yang signifikan antara semua kumpulan dan kedua-dosis zerumbon tidak berkesan terhadap ekspresi protein ChAT. Kesimpulannya, zerumbone menunjukkan peningkatan dalam proses pembelajaran sambil mengurangkan hiperaktif, kegelisahan / kemurungan, dan aktiviti enzim ACHE dalam tikus pra-dirawat scopolamine. Oleh itu, zerumbon boleh menjadi calon yang baik untuk merawat tingkah laku demensia. Walau bagaimanapun, lebih banyak penyelidikan perlu dilakukan untuk mengetahui mekanisme tindakannya.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABC	ATP-Binding Cassette transporter
ACh	Acetylcholine
AChE	Acetyl Cholinesterase
AD	Alzheimer's disease
AGE	Advanced Glycation End-products
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
Aβ	Amyloid β
BQCA	Benzyl Quinolone Carboxylic Acid
BuChE	Butyrylcholinesterase
Ca^{2+}	Calcium Ion
cAMP	Cyclic Adenosine Monophosphate
CD2AP	CD2-Associated Protein
ChAT	Choline Acetyltransferase
ChEIs	Cholinesterase Inhibitors
CHT1	Choline Transporter 1
Cl^-	Chloride Ion
CNS	Central Nervous System
COX2	Cyclooxygenase-2
DHA	Dacosahexaenoic Acid
EPA	Eicosapentaenoic Acid
fAD	Familial Alzheimer's Disease
GABA	Gama Aminobutyric Acid
GAD	Generalized Anxiety Disorder
GSK-3β	Glycogen Synthase Kinase 3 Beta
HPA	Hypothalamic Pituitary Adrenal
i.p.	Intraperitoneal
IL-1b	Interleukin-1b
IUP	Intrinsically Unstructured Protein
K^+	Potassium Ion
LTP	Long-Term Potentiation
mAChR	Muscarinic Acetylcholine Receptor
MCI	Mild Cognitive Impairment
MDD	Major Depressive Disorder
mPFC	Medial Prefrontal Cortex
$Na^=$	Sodium Ion
nAChR	Nicotinic Acetylcholine Receptor
NFT	Neurofibrillary Tangle
NF-κB	Nuclear Factor Kappa-B Cells
NGF	Nerve Growth Factor
NLS	Nuclear Localization Signals
NMDA	N-Methyl-D-Aspartate
NO	Nitric Oxide
OCD	Obsessive Compulsive Disorder
PHF	Paired Helical Filaments
PICALM	Phosphatidylinositol- Binding Clathrin Assembly Protein
PKC	Protein Kinase C

PNS	Peripheral Nervous System
PTSD	Posttraumatic Stress Disorder
PVDF	Polyvinylidene Fluoride
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SAD	Social Anxiety Disorder
sAD	Sporadic Alzheimer's Disease
SNRI	Serotonin and Norepinephrine Reuptake Inhibitors
SP	Specific Phobia
SSRI	Selective Serotonin Reuptake Inhibitors
TNF	Tumor Necrosis Factor
VAChT	Vesicular Acetylcholine Transporter

CHAPTER 1

INTRODUCTION

1.1 General overview

Dementia is defined as progressive or chronic dysfunction of sub-cortical and cortical function that causes complex cognitive deterioration. Cognitive alterations are usually together with behaviour, mood, and personality disturbances. Often, a difference exists between dementia with Lewy bodies, primary degenerative dementias like Alzheimer's disease, secondary dementia to other disease process, such as AIDS dementia and frontotemporal dementia (Gratuze et al., 2016).

A progressive neurodegenerative disease, Alzheimer's disease (AD) is characterized by cognitive deterioration associated with deteriorating activities of daily living and behavioural disorders (Terracciano and Sutin, 2019). AD is the main cause of dementia comprising almost 70% of worldwide cases of dementia (Reitz et al., 2011). Granulovascular degeneration, neurofibrillary tangles and senile plaques are the classic pathogenic triad of AD. Besides, the activity of acetylcholinesterase (AChE) enzyme which is a key enzyme in breaking down of acetylcholine (ACh) will be increased and cause to decrease brain's ACh level in AD patients. Reportedly, a strong correlation exists between the lower level of ACh and the degree of cognitive impairment. Some neuropsychiatric symptoms including struggle in learning and recalling new information, memory loss, anxiety, depression, perception disorders, agitation and aggression have some pathogenic processes with AD beside their unique pathogenic processes (Nishteswar et al., 2014).

Five drugs were introduced since 1993 for managing AD. Currently, AD is treated with N-methyl-D-aspartate receptor blockers (Rodríguez-Ruiz et al., 2017) and cholinesterase inhibitors (ChEIs) (Potter and Kerecsen, 2017; Rogers and Friedhoff 1996; Rösler et al., 1999). Despite numerous research studies, these treatments are said to have merely 'symptomatic' effects rather than 'disease-modifying', yet this distinction is controversial (Apostolova, 2016). As such, existing medications do not treat AD, but probably stabilize or lessen symptoms and signs of AD for a short time. Currently, not many symptomatic treatment choices are available (Heo et al., 2011).

Plant-derived compounds are significant source of many synthetic drugs. A sesquiterpenoid called Zerumbone is found in large in the stems of *Zingiber zerumbet (L) Smith;* a subtropical ginger plant. Experiments have shown anti-carcinogenic activities of some dietary terpenoids. Zerumbone could prevent proliferation of breast (Kirana et al., 2003) and colon (Murakami et al., 2002) cancers, suppress skin tumours in mice (Murakami et al., 2004), block FaDu (human squamous cell carcinoma cell line), KBM-5 (human myeloid), activation of TNF-induced NF-κB in H1299 (lung adenocarcinoma), and A293 (human embryonic kidney) cells (Takada et al., 2005). The *in vitro* study of zerumbone has shown that it has the potential to inhibit

acetylcholinesterase enzyme and could be a great source of anti-AD agent (Rahman et al., 2014).

In this study, scopolamine-induced memory deficits which is included in chemically induced animal models, was used to determine the properties of zerumbone against dementia by investigating the behaviour using several methods, AChE enzyme activity and expression of choline acetyltransferase (ChAT) protein in the brain of Sprague Dawley (SD) rats pre-treated with scopolamine hydrobromide. Scopolamine is an anti-cholinergic drug which is frequently used to induce memory deficit for experimental purpose. Scopolamine acts as a competitive antagonist at muscarinic receptors in the cerebral cortex. It blocks ACh binding sites and cause to release ACh in high concentration and results in damaging of the hippocampus nerves. This eventually leads to memory loss and learning problems (Sodhi et al., 2014).

1.2 Research problem and justification

Insufficient amount of acetylcholine in the brain is considered as one of the major AD risk factors. However, dozens of AChE inhibitors drugs prescribed to slow or stop neuronal malfunction and death but they are not effective in patients due to their resistance, adverse effects, and poor efficacy. Unlike synthetic medicines, some herbal medicine could be more effective to inhibit AChE enzyme with lesser adverse effects. Zerumbone, a neutral bioactive compound, was used in the present study to inhibit AChE enzyme in scopolamine pre-treated rat's brain.

1.3 Hypothesis

Zerumbone has the potential to improve symptoms of dementia in the scopolamine-induced dementia rats.

1.4 Research objectives

1.4.1 General objective

To investigate the effect of zerumbone against scopolamine-induced dementia in rats.

1.4.2 Specific objectives

1. To establish the dementia animal model
2. To investigate the effect of zerumbone on hyperactivity, anxiety, depression and memory impairment in scopolamine-induced dementia rats.
3. To evaluate the inhibition of AChE enzyme activity by zerumbone in scopolamine-induced dementia rat's brain.
4. To determine the down or up regulation of ChAT protein expression by zerumbone in scopolamine-induced dementia rat's brain.

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