UNIVERSITI PUTRA MALAYSIA

NEUROPROTECTIVE PROPERTIES OF Centella asiatica (L.) URBAN ON CHRONIC UNPREDICTABLE MILD STRESS INDUCED MALE WISTAR RATS

SARAVANAN JAGADEESAN

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By

SARAVANAN JAGADEESAN

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

August 2020

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DEDICATION

This work is dedicated to my

Father: Dr. M.L.Jagadeesan, Mother (Late): Dr. (Mrs).Sarojini Jagadeesan,

Wife: Mrs. Rajalakshmi Saravanan, Children: Shivasuriya Saravanan and Omkar Saravanan

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

NEUROPROTECTIVE PROPERTIES OF *Centella asiatica* (L.) Urban ON CHRONIC UNPREDICTABLE MILDS STRESS INDUCED MALE WISTAR RATS

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August 2020

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

Stress could have a major impact on the physiology and psychology of an individual. Stress can be viewed from the perspective of duration as acute and chronic. The chronic stress has a major role in the aetiopathogenesis of several neuropsychiatric conditions primarily depression. The characteristic hyper-responsiveness of glucocorticoids in these situations have an influence on the ultrastructural and biochemical functions of the neurons of the hippocampus and prefrontal cortex. The presently available medications for the management of depression have multiple limitations. They generally have long latency for positive results, are not universally suitable and have multiple adverse effects. These factors encourage the need for innovative pharmaceuticals which could override these deficiencies. The most promising source for such novel molecules are the herbs used in traditional medicines. *Centella asiatica* (CA) has historically prominent use in traditional medicine for its putative neuroprotective and neuro-regenerative properties. Extracts of CA were assessed in chronic stress induced rats and the results analysed. Healthy male Wistar rats of age between 8 – 10 weeks were procured and maintained under laboratory conditions. The rats were held in six groups. One group was a control. Chronic unpredictable mild stress was administered to the rest of the groups. The mild stress was delivered by restrainers, forced swimming in cold water, an overnight food and water deprivation, placement on wet bedding, placement in cage tilt, tail pinching, overcrowding the cages and changing the cage mates. These unpredictable stress were randomly delivered over 64 days. One of the group subjected to these stresses was retained as model group. The rest of the groups were administered with crude extracts of CA at the doses of 200 mg/kg, 400 mg/kg, 800 mg/kg, while one group received fluoxetine (Flx) 10 mg/kg body weight. The aforementioned medications were administered daily for 64 days, 30 minutes before the commencement of experiment. Following the sixty-four days of experiment, behavioural test including

Forced Swim Test (FST), Open Field Test (OFT), Elevated Plus Maze Test (EPM) And T-Maze Test were performed. At the completion of these behavioural test, the rats were euthanised and the brain tissue were collected and blood samples obtained. The neural tissue were analysed using Nissl's stain and transmission electron microscope (TEM). The neural tissues were also quantitatively assessed for malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT) and acetylcholinesterase (AChE). Polymerase chain reaction (PCR) was done to identify the genes for mSOD and mCAT. The blood samples were assessed for quantitative estimation of cortisol levels. The rats which received CA extract were compared with the stress model group of rats. The rats receiving CA showed less impact on behaviour, while the Nissl's staining revealed a higher number and density of viable neurons of hippocampus. The rats which received CA extract at dosages of 400 and 800 mg/kg had significantly less ultrastructural alterations in the mitochondria, nucleus, synapse and myelin sheath. In the same rat groups, MDA (oxidative stress protein) was significantly lesser and the levels of SOD and CAT (antioxidant) were higher. The levels of cortisol and AChE were significantly lesser than in the stress model group. The efficacy of CA was similar to Flx. In conclusion CA effectively prevents the changes in behaviour, neuronal ultrastructure, levels of AChE and oxidative stress biomarkers due to chronic stress in the brain and mitigates cortisol release. CA could prove an useful agent for use in the long term prevention of neurologic and behavioural changes in stress.

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

CIRI-CIRI NEUROPROTEKTIF *Centella asiatica* (L.) Urban TERHADAP TIKUS YANG DIARUH STRES KRONIK

Oleh

SARAVANAN JAGADEESAN

Ogos 2020

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

Stres mempunyai impak yang besar terhadap fisiologi dan psikologi individu. Stres boleh diklasifikasikan mengikut tempoh masa iaitu stres akut dan kronik. Stres kronik memainkan peranan yang utama di dalam etiopatogenesis beberapa penyakit psikiatri neuro terutamanya depresi. Ciri keresponsifan yang hiper terhadap glukokortikoid akan mengakibatkan perubahan pada ultrastruktur dan fungsian biokimia neuron di hipokampus dan korteks prefrontal. Ubat yang digunakan untuk merawat depresi pada masa ini mempunyai limitasi yang pelbagai. Secara umumnya ia mempunyai tempoh latensi yang panjang untuk kesan yang positif. Walaubagaimanapun ia tidak sesuai secara universal dan mempunyai kesan sampingan yang pelbagai. Oleh yang demikian, inovasi di dalam farmaseutikal adalah perlu untuk mengatasi permasalahan tersebut. Salah satu sumber untuk molekul yang novel adalah dari herba perubatan tradisional.

Herba *Centella asiatica* (CA) telah digunakan sekian lamanya di dalam perubatan tradisional berdasarkan ciri-cirinya yang bersifat melindungi dan meransang pertumbuhan neuron. Ekstrak CA digunakan untuk menilai peranannya didalam merawat tikus yang teraruh dengan stres kronik. Kajian menggunakan tikus Wistar jantan yang sihat dan berusia 8 ke 10 minggu. Tikus kajian diletakkan dibawah keadaan makmal yang piawai dan dibahagikan kepada enam kumpulan. Satu kumpulan adalah kumpulan kawalan. Kumpulan haiwan yang lain didedahkan kepada stres sederhana yang tak terduga.

Stres sederhana yang tak terduga adalah seperti berikut, penghalang pergerakan, renangan paksaan di dalam air sejuk, tanpa makanan dan minuman untuk semalaman, sangkar yang basah, kedudukan sangkar yang senget, ekor terpicit, kesesakan di dalam sangkar, dan saling pertukaran tikus antara sangkar. Kesemua stres tak terduga ini

dipilih secara rawak untuk aruhan stres selama 64 hari. Salah satu kumpulan yang didedahkan kepada stres tak terduga dikekalkan sebagai kumpulan tikus model stres. Manakala kumpulan yang lain menerima rawatan ekstrak mentah CA yang berdos 200 mg/kg, 400 mg/kg dan 800 mg/kg, serta satu kumpulan kawalan positif yang menerima rawatan fluoxetine 10 mg/kg (Flx). Kesemua rawatan tersebut dilakukan selama 64 hari dan administrasi harian dilaksanakan 30 minit sebelum sesuatu eksperimen. Ujian Renangan Paksaan (FST), Ujian Lapangan Terbuka (OFT), Ujian Sesat Palang Terangkat (EPM) dan Ujian Pagar Sesat T dilakukan selepas tempoh rawatan selama 64 hari. Persampelan tisu otak dan darah dilakukan selepas tikus dieutanasia sejurus menamatkan ujian-ujian tingkahlaku tersebut. Tisu otak yang diwarnakan oleh pewarna Nissl dianalisa menggunakan mikroskop transmisi elektron (TEM). Analisis malondialdehid (MDA), superoksik dismutase (SOD), katalase (CAT) dan asetilkolinesterase (AChE) pada sampel otak turut diukur. Pengenalpastian gene-gen untuk mSOD dan mCAT dilakukan menggunakan kaedah reaksi rantai polimerase (PCR). Aras kuantitatif kortisol di dalam darah turut diukur. Tikus yang menerima rawatan CA dibandingkan dengan tikus model stres. Tikus yang menerima rawatan CA mempamerkan impak tingkahlaku yang lebih baik dan perwarnaan Nissl menunjukkan pertambahan bilangan dan kepadatan neuron di hipokampus. Tikus yang menerima rawatan CA juga menunjukkan perubahan yang sedikit pada ultrastruktur mitokondria, nukleus, sinaps dan sarung mielin. . Pada masa yang sama, aras MDA (protein stres oksidatif) adalah berkurangan dan aras SOD dan CAT (antioksidan) adalah lebih tinggi. Manakala aras kortisol dan AChE adalah lebih rendah berbanding kumpulan tikus model stres. Hasil kajian menunjukkan efikasi CA adalah setara dengan Flx. Kesimpulan dari hasil kajian menunjukkan CA adalah efektif untuk menghalang perubahan-perubahan tingkahlaku, ultrastruktur neuron, aras AChE dan biopenanda stres oksidatif yang disebabkan oleh stres kronik dan mengurangkan penghasilan kortisol. Oleh yang demikian, CA berpotensi sebagai agen pencegah yang efektif untuk mengelakkan perubahan neurologik dan tingkahlaku yang disebabkan oleh stres.

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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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LIST OF ABBREVIATIONS

AChE	Acetylcholinesterase
ANOVA	Analysis of variance
APA	American Psychiatric Association
BDNF	Brain-derived neurotrophic factor
CA	Centella asiatica
CA3	Cornu ammonis 3
CAT	Catalase
Cm	Centimetre
CMD	Chronic Major Depression
CREB	cAMP-response element binding protein
CUMS	Chronic unpredictable mild stress
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELISA	Enzyme labelled immunosorbent assay
EM	Electron microscopy
EPM	Elevated plus maze
Flx	Fluoxetine
FST	Forced swimming test
GAS	General adaptation syndrome
GSH	Glutathione
h	Hour
HPA	Hypothalamo pituitary adrenal
Kg	Kilogram
MCI	Mild cognitive impairment
Mg	Milligram

Min	Minutes
NHMS	National Health Morbidity Survey
NMDA	N-methyl-d-aspartic acid
OFT	Open field test
OS	Oxidative stress
PBS	Phosphate buffered saline
ROS	Reactive oxygen species
RT-PCR	Reverse transcriptase – polymerase chain reaction
S	Stressor
SD	Standard deviation
SNS	Sympathetic nervous system
SOD	Superoxide dismutase
SSRI	Selective serotonin re-uptake inhibitors
TEM	Transmission electron microscopy
T-maze test	T-maze spontaneous alternation test
USA	United States of America
WHO	World health organisation

CHAPTER 1

INTRODUCTION

1.1 Background

Depression is a widely prevalent disorder among humans associated with exposure to stressful life events, and it is defined by the American Psychiatric Association (APA) as a condition characterised by the presence of sad, empty, or irritable mood, along with physical and cognitive changes that significantly impair the capacity of an individual to function normally (American Psychiatric Association, 2013). Depression, which is the outcome of chronic stress exerts huge financial burden on society and healthcare.

Stress is a process where the physical and psychological demands on an individual, which are called the stressors, affect the ability of the individual or organism to adapt to the ensuing challenges (Cano-López & González-Bono, 2019a). The different types of stressors are 1) acute and chronic 2) major and minor and 3) desirable and undesirable, highlight the various stress related aspects of life. Chronic stress occurs when the stressors are persistent or repetition of an initial stressful event (Segerstrom & Miller, 2004).

Studies on post-mortem brain tissues of humans with chronic stress induced depression, and also on animal models of depression, have demonstrated reductions in the size of parts of the limbic system of the brain such as hippocampus and amygdala, that regulates mood and cognition (Masi & Brovedani, 2011). It was further observed that there was a reduction in neuronal synapses, which play a significant role in the pathogenesis of depression. Oxidative stress has been reported to be a significant factor in the pathogenesis of depression in humans (Ng et al, 2008). The close interaction of nitrosative and oxidative stress has also been demonstrated to be involved in the pathogenesis of depression (Maes et al, 2011a), while circadian rhythm changes have also been shown to produce depression (McClung, 2011). Since chronic stress plays an important role in the causation of depression (Jelovac et al, 2013), rat models of depression could be developed by subjecting the rats to chronic unpredictable mild stress (CUMS) (Qiao et al, 2016).

Centella asiatica (CA) is a green leafy herb which is extremely valued for its medicinal properties and has been used in the traditional medicines of many countries since ancient times (Sabaragamuwa et al, 2018a). CA has been used in various traditional medicines for its memory enhancing effects (Orhan, 2012), and also for its ability to act as a revitalizer for nerves and brain cells (Seevaratnam, 2012). The health benefits of CA have been reported historically in Unani medicine in Sri Lanka, Ayurvedic medicine in India, Chinese traditional medicine, folk medicine in South Asian countries and in African traditional medicine (Jahan et al., 2012).

In all the aforementioned traditional medicinal practices, CA has also been used for the treatment of headache and leprosy (Shukla et al, 1999) wound healing and memory enhancement (Sari et al, 2014). Further, the ameliorative effects of CA on d-galactose and aluminium chloride induced oxidative stress and cholinergic dysfunction causing neuronal degeneration, and cognitive impairment in male Wistar rats (Chiroma et al, 2019a) and lead induced toxicity in rats (Sainath et al, 2011) have also been documented. Most studies involving rat models of depression were performed on Wistar rats.

1.2 Problem statement

Depression is one of the leading causes of disability affecting millions of people worldwide. The prevalence of depression has been reported to be approximately 15% of the population in the developed countries resulting in notable personal suffering, substantial economic loss and significant social burden (Kessler & Bromet, 2013). It has been stated that in recent years, there has been an increase in the prescription of antidepressants worldwide that act by interacting with norepinephrine and serotonin neurotransmitter systems as a single therapy. These drugs have limitations, as it takes several weeks for the onset of therapeutic effect and are only effective in approximately 33% of patients with depression (Craighead & Dunlop, 2014). Further, certain antidepressant drugs are often associated with extrapyramidal side effects, including abnormal electrical activity of heart, increase in body weight, hyperlipidaemia and hyperglycaemia, among other adverse side effects (Spindelegger et al, 2014). Hence, it is of paramount importance to search for alternate antidepressants with better efficacy and lesser side effects.

1.3 Justification for the present study

The CUMS is a classic protocol used for the induction of cognitive impairment and depression-like behaviour in rat models, as well as for studying their underlying pathophysiological mechanisms (Jia et al, 2017). Additionally, the hippocampus of the rat brain is sensitive to CUMS, and hence hippocampal dysfunctions, like cognitive and mental deficits have been exhibited by rats subjected to the CUMS (Stockmeier et al, 2004). However, the number of stressors used and the duration of time for the CUMS induction varies among researchers for understanding of CUMS pathology and for screening of potential antidepressant drugs.

Asiaticoside, a major phytochemical compound of CA, which has been used in traditional medicine has shown promising anxiolytic (Chen et al, 2006) and antidepressant (Liang et al, 2008) effects among acute stress induced rat models. Triterpenes present in CA leaves have shown promising antidepressant effects as observed in the forced swim test (FST), used to study acute depression model in rats (Chen et al, 2005). However, no studies have been performed using CA in the prevention of CUMS-induced depressive behaviour and associated changes in the brains of rat models.

The present research has been conceptualised based on the possible attenuation of depression in CUMS-induced rats by CA extract **(Figure 1.1**). This study observed the changes in the cortisol levels and the modulation of cholinergic and oxidative stress pathways. The present study also explores the potential use of CA in preventing apoptosis by blocking the intrinsic mitochondria-mediated apoptotic pathway in experimental rat models. Finally, the protective effects of CA on morphological alterations in the brains of rat models were also explored in the present study.

1.4 Hypothesis

- CA prevents cognitive impairment in CUMS-induced rat depression in male Wistar rats
- CA prevents neuronal degeneration and ultrastructure changes in CUMS-induced depression in male Wistar rats

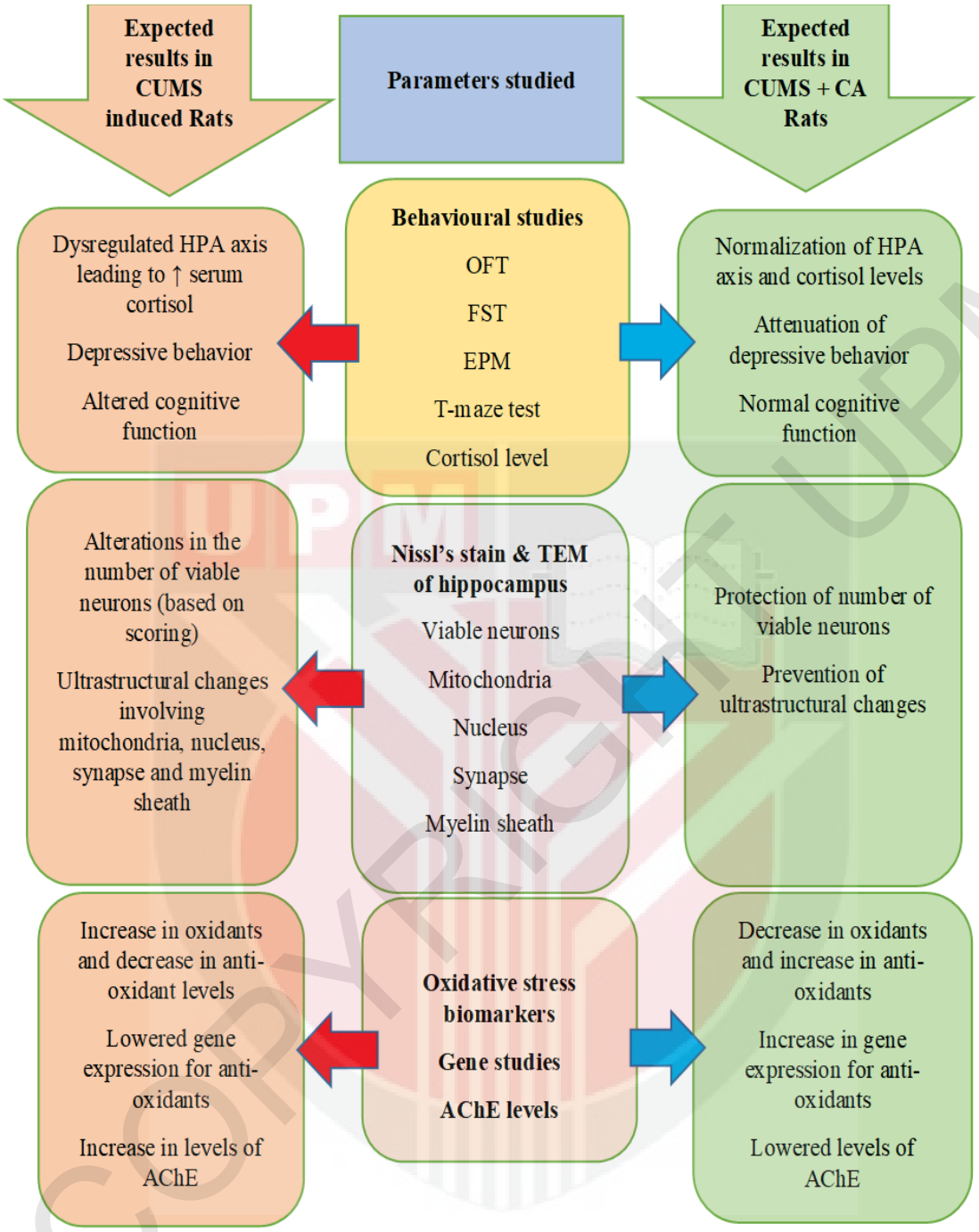
1.5 Objectives of the study

1.5.1 General objective

The general objective of the present study was to investigate the neuroprotective potentials of CA extract in CUMS-induced depression in male Wistar rats.

1.5.2 Specific objectives.

i. To evaluate the behaviour of CUMS-induced depression in the rat model, pre-treated with CA.
ii. To assess the ultrastructural changes in the brain of CUMS-induced depression in rat model, pre-treated with CA.
iii. To measure selected biochemical parameters, i.e., cortisol, MDA, SOD, CAT and AChE in CUMS-induced rat model of depression, pre-treated with CA.



* CUMS: Chronic unpredictable mild stress includes 24-hours of food deprivation, 24-hours of water deprivation, 5-minutes of cold water swimming (at 5°C), change of cage mates for 12-hours, tail pinch, 12-hours of cage tilt (at 45° angle), 12-hours overcrowding, 12-hours of wet bedding and 4-hours of physical restrain.

Figure 1.1 : Conceptual design for neuroprotective effect of CA on CUMS* induced rats

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