**UNIVERSITI PUTRA MALAYSIA**

# *ANTI-INFLAMMATORY EFFECT OF Ficus deltoidea JACK EXTRACT IN BEHAVIORAL AND CELLULAR MODELS OF DEPRESSION*

**WANG HUILING**

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# ANTI-INFLAMMATORY EFFECT OF *Ficus deltoidea* JACK EXTRACT IN BEHAVIORAL AND CELLULAR MODELS OF DEPRESSION

By

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Doctor of Philosophy

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By

**WANG HUILING**

**February 2017**

**Chairman : Associate Professor Mohamad Taufik Hidayat Baharuldin, PhD**
**Faculty : Medicine and Health Sciences**

Depression, a worldwide mental disease, brings an enormous burden to the patients and their families. Current treatments for depression are far from satisfactory. It is required to develop the novel antidepressants from the natural medicines which are good antidepressants with less side effects. Many hypotheses have been put forward to clarify the origins of depression. The inflammatory hypothesis points to the significant role of psychoneuroimmunological dysfunctions. Anti-inflammatory therapy is receiving closer attention. *Ficus deltoidea* (FD) is one of the well-known traditional medicinal plants in Malaysia. Phenolics and flavonoids are the major components responsible for its antioxidant and anti-inflammatory effects. The present study was carried out to investigate the antidepressant-like effect and the anti-inflammatory properties of FD extract by *in vivo* and *in vitro* method respectively.

*In vivo* antidepressant-like potential of FD extract was evaluated by the alterations of body weight and behaviors induced by chronic unpredictable mild stress (CUMS). Oral administration of FD significantly ameliorated the decreased body weight and depressant-like behaviors induced by CUMS which included reduced sugar intake, decreased score of open field test (OFT), and increased immobility time in forced swimming test (FST). FD administration also decreased the amount of pyknotic and dark stained hippocampal neurons of depressed rats. *In vitro* anti-inflammatory effects of FD extract were assessed by the production of inflammatory mediators and the changes of morphology which were induced by lipopolysaccharide (LPS) in BV2 cell line. FD pretreatment showed significant inhibitory effects on the release of nitric oxide (NO) and tumour necrosis factor (TNF)-α, the expression of inducible nitric oxide synthase (iNOS) and CD40 from LPS-activated BV2 cells. FD pretreatment also attenuated the morphological changes of microglia induced by LPS. FD-pretreated conditioned medium was

transferred from BV2 cells to N2A cells. It was proved through immunocytochemical staining and MTS assay that FD-pretreated conditioned medium decreased the neuronal damage induced by LPS.

The above results suggest that FD treatment ameliorates the behavioral alterations induced by CUMS, significantly inhibits LPS-induced microglia activation and the release of inflammatory mediators and possesses neuroprotective effects. The mechanism of antidepressant-like activity of FD may therefore be due to its anti-inflammatory and neuroprotective property.

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

**KESAN ANTI- RADANG EKSTRAK FICUS DELTOIDEA JACK KE ATAS MODEL KEMURUNGAN DI PERINGKAT TINGKAH LAKU DAN SEL**

Oleh

**WANG HUILING**

**Februari 2017**

**Pengerusi : Profesor Madya Mohamad Taufik Hidayat Baharuldin, PhD**
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Depresi adalah penyakit mental yang melanda seluruh dunia. Depresi mendatangkan beban yang berat kepada pesakit dan keluarga mereka. Rawatan semasa bagi penyakit depresi adalah kurang memuaskan. Oleh itu, pembangunan ubat anti depresi dari sumber semulajadi yang baik dan mempunyai kurang kesan sampingan adalah perlu. Terdapat pelbagai hipotesis yang telah diutarakan untuk menerangkan punca depresi. Hipotesis radang menyatakan peranan yang signikan oleh kegagalan fungsi *psychoneuroimmunological*. Terapi anti-radang kini sedang mendapat perhatian yang tinggi. *Ficus deltoidea* (FD) adalah antara tumbuhan herba ynag dikenali di Malaysia. Phenolics dan flavonoids adalah komponen utama yang bertanggungjawab untuk kesan antioksida dan anti-radangnya. Kajian ini dijalankan untuk menyiasat kesan anti-depresi dan keupayaan anti-radang oleh ekstrak FD dengan menggunakan kaedah *in vivo* dan *in vitro*. Penialaian *in vivo* potensi anti-depresi oleh ekstrak FD dilakukan melalui perubahan berat badan dan tingkahlaku yang disebabkan oleh stress sederhana kronik yang tidak dijangka (CUMS). Pemberian FD secara oral menghilangkan kesan pengurangan berat badan dan tingkahlaku yang disebabkan oleh CUMS, seperti pengurangan pengambilan gula, penurunan skor ujian lapangan terbuka (OFT) dan meningkatkan masa tidak bergerak dalam ujian berenang paksaan (FST). Pemberian FD kepada tikus yang mengalami depresi juga menurunkan jumlah neuron hippokampus yang piknotik dan diwarnakan gelap. Kesan anti-radang melalui kaedah *in vitro* dinilai melalui penghasilan mediator-mediator radang dan perubahan morfologi yang disebabkan oleh lipopolisakarida (LPS) terhadap sel BV2. Pra-rawatan FD menunjukkan pengurangan yang signifikan dalam pembebasan nitrik oksid (NO) dan faktor nekrosis tumor )TNF)-α, ekspresi *inducible nitric oxide synthase* (iNOS) dan CD40 dari sel BV2 yang diaktifkan oleh LPS. Pra-rawatan FD juga menyebabkan perubahan morfologi mikroglia yang disebabkan oleh LPS. Media yang telah di pra-rawat oleh FD dipindah dari sel BV2 kepada sel N2A. Melalui pewarnaan immunositokimia dan ujian MTS, ianya

terbukti bahawa media yang telah di pra-rawat oleh FD mengurangkan kerosakan neuron yang disebabkan oleh LPS. Keputusan-keputusan di atas mencadangkan bahawa rawatan FD meredakan perubahan tingkahlaku yang disebabkan oleh CUMS, menghalang LPS daripada mengaktifkan mikroglia, membebaskan mediator-mediator radang dan mempunyai kesan perlindungan neuron. Oleh itu, mekanisma antidepresi oleh FD mungkin disebabkan oleh keupayaan anti-radang dan perlindungan neuron.

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I certify that a Thesis Examination Committee has met on 27 February 2017 to conduct the final examination of Wang Huiling on her thesis entitled "Anti-Inflammatory Effect of *Ficus deltoidea* Jack Extract in Behavioral and Cellular Models of Depression" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

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| | |
|---|---|
| % | percent |
| ± | plusminus |
| α | alpha |
| ℃ | degree Celsius |
| L | litre |
| mL | millilitre |
| µL | microliter |
| g | gram |
| mg | milligram |
| µg | microgram |
| mg/mL | milligram per millilitre |
| µg/mL | microgram per millilitre |
| g/L | gram per litre |
| U/mL | unit per millilitre |
| RT | room temperature |
| h | hour |
| min | minute |
| s | second |
| ACTH | adrenocorticotropic hormone |
| BBB | blood brain barrier |
| BDNF | brain-derived neurotrophic factor |
| CNS | central nervous system |
| $CO_2$ | carbon dioxide |

| | |
|---|---|
| COX | cyclooxygenase |
| CRH | corticotropin releasing hormone |
| CSF | cerebrospinal fluid |
| CUMS | chronic unpredictable mild stress |
| DAPI | 4',6-diamidino-2-phenylindole dihydrochloride |
| $dH_2O$ | distilled water |
| $ddH_2O$ | double distilled water |
| DMEM | Dulbecco's modified eagle medium |
| DMSO | dimethyl sulphoxide |
| EDTA | ethylenediamine tetra acetic acid |
| ELISA | enzyme linked immunosorbent assay |
| ERKs | extracellular-signal-regulated kinases |
| FBS | fetal bovine serum |
| FD | *Ficus deltoidea* |
| FITC | fluorescein isothiocyanate |
| FST | forced swimming test |
| GSH | glutathione |
| GTP | guanosine triphosphate |
| HE | hematoxylin-eosin |
| HPA | hypothalamic pituitary adrenal |
| 5-HT | 5-hydroxytryptamine |
| IDO | indoleamine 2,3-dioxygenase |
| IFN-γ | interferon gamma |
| IKK | IkappaB kinase |
| IL | interleukin |

| | |
|---|---|
| iNOS | inducible nitric oxide synthase |
| JNK | Jun N-terminal kinase |
| KA | kynurenic acid |
| KYN | Kynurenine |
| LPS | lipopolysaccharide |
| MAPK | mitogen-activated protein kinase |
| mRNA | messenger RNA |
| MTS3 | (4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)- 2H-tetrazolium |
| NE | norepinephrine |
| NF | nuclear factor |
| NMDA | N-methyl-D-aspartic acid |
| NO | nitric oxide |
| $NO_2^-$ | nitrite |
| NOS | nitric oxide synthase |
| NTFs | neurotrophic factors |
| $O_2^-$ | superoxide anion |
| OFT | open field test |
| 3-OH-KYN | 3-hydroxy-kynurenine |
| $ONOO^-$ | peroxynitrite |
| PBS | phosphate buffered saline |
| PFA | paraformaldehyde |
| PG | prostaglandin |
| PI | propidium iodide |
| PTIO | 2-phenyl-4,4,5,5,-tetramethylimidazoline-1-oxyl 3-oxide |

| | |
|---|---|
| QUIN | quinolinic acid |
| ROS | reactive oxygen species |
| RNS | reactive nitrogen species |
| SPT | sucrose preference test |
| SSRIs | selective serotonin reuptake inhibitors |
| TGF-β | transforming growth factor beta |
| TH | tyrosine hydroxylase |
| TNF | tumour necrosis factor |
| WHO | the World Heath Organization |

# CHAPTER 1

## INTRODUCTION

Depression is a common, debilitating and life-threatening mental disorder with a very high prevalence, which has enormous consequences on a patient's life quality. The annual prevalence of depression is 7% and the lifetime prevalence is 16% (Kessler et al., 2005a; Kessler et al., 2005b). It is reported that depression will become the second contributor to the global disease burden by 2020, according to the World Health Organization (WHO) (Menken et al., 2000). The core symptoms of depression are characterized by weight loss, low morale, anhedonia and disrupted sleep (Hurley et al., 2013). Current treatments for depression mainly target the serotonin and/or norepinephrine systems. The curative effects are far away from satisfactory, which primarily reflected in slow work (weeks to months), low efficiency (only one-third of patients achieve full remission of their depressive symptoms and gain functional recovery) and many side effects (insomnia, headache, anxiety) (Skolnick, 2002). Therefore, it is required to identify the systems which may represent novel targets for antidepressants.

Central nervous system (CNS) was thought to be an immune privileged organ before. However, the CNS exhibits features of inflammation in response to infection, injury or disease and contains a resident population of macrophages known as microglia. It was also recently revealed that the CNS contains lymphatic vessels (Louveau et al., 2015). Inflammation within CNS is an important element of pathogenesis in degenerative disorders and some psychiatric diseases, such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis (Liu and Hong, 2003). Microglia are the main cells of the CNS responsible for initiating and propagating inflammatory responses. They are extremely sensitive to any disturbances in the CNS and generally take on an amoeboid shape and release proinflammatory cytokines, chemotactic factors, reactive oxygen species (ROS) and reactive nitrogen species (RNS) when activated. Their inflammatory responses contribute to neuronal damage and results in a self-propelling cycle of neuronal death (Block & Hong, 2005).

Growing evidence suggests neuroinflammation plays an important role in the pathogenesis of depression. Patients received immunotherapy typically showed depressed symptoms (Anisman et al., 2007). Most of antidepressants possess certain anti-inflammatory effects (Janssen et al., 2010). Animal models of depression based on inflammation is developed now. Increased biomarkers of inflammation are detected in both depressed animals and patients (Dowlati et al., 2010; Xu et al., 2015). Proinflammatory cytokines have been proved to be associated with many pathophysiological domains which characterize depression, including neuroendocrine function (McTigue & Tripathi, 2008; Rajkowska & Miguel-Hidalgo, 2007), neurotransmitters metabolism (Zhu et al., 2006; Moron et al., 2003; Pace et al., 2007), synaptic plasticity (Spiegel et al., 2006) and behavior

(Ben et al., 2008). Inflammatory, oxidative and nitrosative pathways have become a novel target for the development of antidepressants (Maes, 2008). The occurrence of depression may be due to the increased release of proinflammatory cytokines from activated microglia according to the cytokine hypothesis (Yang et al., 2014). Therefore, drugs with the capability to inhibit the activation of microglia and the production of cytotoxic mediators would provide neuroprotection and possess anti-depressant effect.

*Ficus deltoidea* (FD) (Mas Cotek), which belongs to Moraceae family, is one of well-known traditional medicinal plants in Malaysia. It is commonly used to treat various kinds of ailments such as sores, wounds, pain and rheumatism. The phenol and 2,4-bis(dimethylbenzyl)-6-t-butylphenol are the major compounds in FD leaf extract (Lee et al., 2011). It was reported that FD possessed antioxidant activity in vitro models (Abdullah et al., 2009; Hakiman & Maziah, 2009) and anti-inflammatory activity (Tantowi et al., 2016; Zakaria et al., 2012; Zunoliza et al., 2009). The aim of this study was to investigate the antidepressant-like effects of FD extract on CUMS-treated rats and its underlying mechanisms.

**General objective**

To clarify the antidepressant-like effects of FD aqueous extract and its underlying mechanisms.

**Specific objectives**

1. To determine the antidepressant-like effect of FD by behavioral tests.
2. To evaluate the neuroprotective effect of FD in CUMS-treated rat.
3. To study the target organ toxicity of FD.
4. To decipher the anti-inflammatory effect of FD by examining the effects of FD pretreatment on NO production, the protein and mRNA expression of iNOS and TNF-α from activated BV2 cells, as well as the number of $CD40^+$ cells, morphology of BV2 cells.
5. To evaluate the neuroprotective effect of FD by the viability of N2A cells in microglia conditioned medium.

**Hypotheses**

1. FD aqueous extract possesses antidepressant-like effect and has no obvious liver and kidney toxicity.
2. The mechanisms of antidepressant-like effect of FD are its anti-inflammatory and neuroprotective potential.

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