UNIVERSITI PUTRA MALAYSIA

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MASTER OF SCIENCE
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By

FARAH IDAYU BINTI NASIR

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, In Fulfilment of the Requirements for the Degree of Master of Science

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Abstract Submitted to Senate of Universiti Putra Malaysia, In Fulfilment of the Requirements for Degree of Master of Science

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Chairman : Mohamad Taufik Hidayat Bin Baharuldin, PhD
Faculty : Medicine and Health Sciences

Major depressions are among the most prevalent disease of the central nervous system with a high morbidity and mortality. Available antidepressants that used as pharmacotherapy for depression produce a lot of adverse effects towards depressed patient. Therefore, safer treatments for treating mental illness like depression are still needed. On the other hand, drugs obtained from natural sources are perceived to have at least risk and low side- effects profiles, while having the ability to cure mental disorder. Mitragynine (MG) is the major alkaloid identified in *Mitragyna speciosa* Korth which has been used in traditional medicine. The antinociceptive action of MG is due to its role on opioid system to stimulate the release of endogenous noradrenaline and serotonin from nerve terminal. However, none has been reported on the mechanism action of MG via spectrum of antidepressant studies. Based on the principle that MG has a significant role in producing antinociceptive action, it might as well beneficial as

antidepressant. Hence, the present investigation evaluated the antidepressant effect of MG in the mouse forced swim test (FST) and tail suspension test (TST) together with its effects on hypothalamic-pituitary-adrenal (HPA) axis by measuring the corticosterone concentration of mice exposed to FST and TST. An open-field test (OFT) was used to study any association of immobility in the FST and TST with psychomotor stimulant effect of MG. Male ICR mice were randomly assigned to six treatment groups (n=8): Group I (vehicle control group), Group II received reference drug 20 mg/kg, fluoxetine (selective serotonin reuptake inhibitor, SSRI), Group III received tricyclic antidepressant drug, amitriptyline hydrochloride 10 mg/kg and Group IV, V and VI received 5, 10 and 30 mg/kg of MG. MG at doses of 10 mg/kg and 30 mg/kg significantly reduced the immobility time of mice in both FST and TST without any significant effect on locomotor (crossing) activity in OFT. Moreover, MG significantly reduced the released of corticosterone in mice exposed to FST and TST at dose of 10 mg/kg and 30 mg/kg.In order to investigate the involvement of MG on cannabinoid system, a group of animals were randomly assigned into four experimental groups (8 mice per group). The groups were consist of group I, that served as control treatment; group II was given MG (10 mg/kg i.p.); group III was given cannabinoid receptor (CB_1) antagonist drug, AM 251 (0.5 mg/kg i.p.) and finally group IV was given pre-treatment of AM 251 (0.5 mg/kg i.p.) followed by treatment of MG (10 mg/kg i.p.). The results showed that pre- treatment of mice with AM 251 produced significant reduction in immobility time as compared with treatment of MG alone and treatment of AM 251 alone. In terms of corticosterone level, pre- treatment of mice with AM 251 significantly increased

the level of corticosterone concentrations as compared with treatment of MG alone and treatment of AM 251 alone after exposed to FST and TST. These data suggest antidepressant effect produced by MG is not likely through its action on cannabinoid receptor system.

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

KESAN ANTI-KEMURUNGAN MITRAGYNINE, ALKALOID DARI *MITRAGYNA SPECIOSA* KORTH, DALAM MODEL KEMURUNGAN MENCIT

Oleh

FARAH IDAYU BINTI NASIR

April 2013

Pengerusi : Mohamad Taufik Hidayat Bin Baharuldin, PhD

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Kemurungan adalah salah satu masalah sistem saraf pusat yang sering dihidapi dengan perkadaran yang tinggi dari segi motiliti dan morbiditi. Dadah anti-kemurungan yang digunakan bagi terapi farmakologi untuk kemurungan menghasilkan banyak kesan sampingan terhadap pesakit yang menghidap kemurungan. Oleh itu, rawatan yang lebih selamat untuk merawat penyakit mental seperti kemurungan masih diperlukan. Ubat-ubatan yang diperolehi daripada sumber semula jadi dilihat mempunyai kurang risiko berbahaya dan kesan sampingan, di samping mempunyai keupayaan untuk menyembuhkan penyakit mental.Mitragynin (MG) adalah alkaloid utama yang dikenalpasti dari tumbuhan *Mitragyna speciosa* Korth di mana ia telah digunakan sebagai ubat tradisional. Kebanyakan penyelidikan lebih tertumpu pada tindakan kesan tahan sakit MG kerana peranannya pada sistem opioid untuk merangsang pembebasan noradrenalin dalaman dan serotonin dari terminal saraf. Berdasarkan pada prinsip bahawa MG mempunyai peranan penting dalam menghasilkan tindakan anti sakit, ia mungkin juga bermanfaat sebagai ubat anti-

kemurungan.Malah banyak kajian telah dilaporkan mengenai kesan dadah anti-kemurungan juga mampu memberikan kesan anti-sakit dan digunakan secara meluas dalam rawatan sakit kronik. Oleh itu, kajian terkini ini menilai kesan anti-kemurungan mitragynin ke atas dua model mencit iaitu ujian paksa-renang (FST) dan ujian penggantungan ekor (TST) juga kesan mitragynin ke atas sistem neuroendokrin iaitu sistem paksi- hipotalamik-pituitari dengan mengukur aras kortikosteron mencit yang terdedah kepada ujian paksa-renang (FST) dan ujian penggantungan ekor (TST). Mencit jantan ICR ditentukan secara rawak kepada enam kumpulan setara (n=8): Kumpulan I (kumpulan kontrol menerima pelarut), Kumpulan II menerima ubat anti-kemurungan yang digunakan sebagai rujukan iaitu 20mg/kg (i.p.) fluoxetine (SSRI), Kumpulan III menerima ubat anti-kemurungan trisiklik ,amitriptyline hidroklorik, 10 mg/kg (i.p.), Kumpulan IV, V,VI menerima mitragynin dos 5, 10 dan 30 mg/kg.Dalam kajian ini, MG pada dos 10 mg/ kg dan 30 mg/kg mengurangkan masa tempoh pegun mencit dalam kedua-dua FST dan TST tanpa kesan signifikan ke atas aktiviti motor dalam ujian lapangan motor (OFT). Selain itu, MG juga merendahkan kadar perembesan kortikosteron mencit yang terdedah kepada FST dan TST pada dos 10mg/kg dan 30mg/kg. Dalam usaha untuk menyiasat penglibatan MG pada sistem cannabinoid, mencit-mencit telah diasingkan secara rawak kepada empat kumpulan eksperimen (n=8). Kumpulan-kumpulan ini terdiri daripada kumpulan I yang berkhidmat sebagai rawatan kawalan; kumpulan II telah diberikan MG (10 mg/ kg i.p.); kumpulan III telah diberi dadah antagonist reseptor cannabinoid (CB_1) AM 251 (0.5 mg / kg i.p.) dan akhirnya kumpulan (IV) telah diberikan pra-rawatan AM 251 (0.5 mg/kg i.p.) diikuti rawatan MG (10 mg/kg). Menurut

keputusan yang terhasil, pra-rawatan tikus dengan AM 251 diikuti MG menghasilkan pengurangan ketara dalam masa pegun mencit berbanding dengan rawatan MG bersendirian dan rawatan AM 251 bersendirian. Dari segi tahap kortikosteron, pra-rawatan tikus dengan AM 251 diikuti MG meningkatkan tahap kortikosteron berbanding dengan rawatan MG bersendirian dan rawatan AM 251 bersendirian selepas terdedah kepada FST dan TST. Data-data ini mencadangkan kesan anti-kemurungan yang dihasilkan oleh MG tidak mungkin melalui tindakan pada sistem reseptor cannabinoid.

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I certify that a Thesis Examination Committee has met on 22 April 2013 to conduct the final examination of Farah Idayu Binti Nasir on her Master of Science thesis entitled "Antidepressant Properties of Mitragynine, An Alkaloid Isolated From *Mitragyna speciosa* Korth, in Mice Model 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 Master of Science (Physiology).

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

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DECLARATION

I declare that this Master thesis is based on my original work except for quotations and citations which have been dully acknowledged. I also declare that it has not been previously, and concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

FARAH IDAYU BINTI NASIR

Date: 22 April 2013

TABLE OF CONTENTS