UNIVERSITI TEKNOLOGI MARA

# NEUROPROTECTIVE ROLE OF AGMATINE AND APIGENIN AGAINST 3-NITROPROPIONIC ACID-INDUCED HUNTINGTON'S DISEASE LIKE SYMPTOMS IN RATS

NOR `AWATIF BINTI OSMANUDIN

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# AUTHOR'S DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Teknologi MARA. It is original and is the results of my own work, unless otherwise indicated or acknowledged as referenced work. This thesis has not been submitted to any other academic institution or non-academic institution for any degree or qualification.

I, hereby, acknowledge that I have been supplied with the Academic Rules and Regulations for Post Graduate, Universiti Teknologi MARA, regulating the conduct of my study and research.

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|---|---|---|
| Name of Student | : | Nor `Awatif binti Osmanudin |
| Student I.D. No. | : | 2015207654 |
| Programme | : | Master of Science (Neuroscience) – PH761 |
| Faculty | : | Pharmacy |
| Thesis Title | : | Neuroprotective Role of Agmatine And Apigenin Against 3-Nitropropionic Acid-Induced Huntington's Disease Like Symptoms In Rats |
| Signature of Student | : | …….. |
| Date | : | December 2021 |

# ABSTRACT

Agmatine is an endogenous neurotransmitter and neuromodulator that emerges as a potential agent to manage diverse central nervous system (CNS) disorders. There is a growing number of preclinical trials indicating the positive impact of exogenous agmatine administration on depression, anxiety, hypoxic ischemia, cognition, opioid resistance, memory, Parkinson's disease, Alzheimer's disease, traumatic brain injury associated alterations/disorders, and epilepsy, along with its neuromodulator and neuroprotective properties. At the same time, apigenin is a flavonoid commonly found in fruits and vegetables and used as a herbal supplement. Antioxidant properties in apigenin have proven to protect neurons from oxidative stress and neuroinflammation. The goal of this research is to test the neuroprotective ability of agmatine and apigenin against 3-nitropropionic acid (3-NP)-induced neurotoxicity in an experimental rat Huntington's disease model. Systemic administration of 3-NP on days 1, 5 and 10 significantly impaired motor activity; rotarod and grip strength test, biochemical parameters (increased lipid peroxidation, accumulation of nitrite, superoxide dismutase reduction, and reduced amounts of glutathione), pro-inflammatory cytokines (increased IL-1β, IL-6 and TNF-a concentrations) and mitochondrial enzymes int the rat brain. Agmatine (80 mg/kg), apigenin (2 mg/kg), and the combination of agmatine (40 mg/kg) and apigenin (1 mg/kg) significantly reduced the time for the rat to fall off from the rotarod and also muscle grip strength. Furthermore, agmatine (80 mg/kg), apigenin (2 mg/kg) and a combination of agmatine and apigenin significantly reduced the level of MDA, nitrite, IL-1β, IL-6 and restored the level of SOD and mitochondrial enzymes level in the rat brain. Agmatine (80 mg/kg) and the combination of both compounds also significantly increase the level of reduced glutathione. However, apigenin exhibited no significant effect in restoring NADH dehydrogenase enzyme and the level of reduced glutathione against 3-NP. These findings suggest that agmatine, apigenin, when given alone at high concentrations or in combination at lower concentrations, offer neuroprotection towards the 3-NP-induced HD-like in the rat model. The possible mechanisms of action involved in this study presumably the modulation of over-stimulated NMDAR that causes excitotoxicity, attenuating the production of NO, oxidative stress, and impairment of mitochondrial enzymes. Another possible mechanism involved is the attenuation of pro-inflammatory cytokines that trigger neuroinflammation.

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