NEW FINDINGS OF DOCTORAL DISSERTATION

Name of Doctoral candidate: **Nguyen Thu Hien**

Dissertation title: **"Study on the anti-dementia and the antidepressant-like effects of *Ocimum sanctum* L. on mice experiments".**

Specialty: **Pharmacology - Clinical pharmacy**

Code of specialty: **9720205**

Name of academic advisors:

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      2. Dr. Le Thi Xoan

Name of academic institute: **National Institute of Medicinal Materials**

Summary of new findings of the dissertation:

1. Experimental model

This study has successfully implemented both the olfactory bulbectomized mice model (OBX) and the unpredictable chronic mild stress-induced depression model (UCMS) in Vietnam. The research has found some new valuable points as follows:

- The OBX model has met three main requirements of the dementia and depression model, including 1) the similarities between the behavior of the animal and the symptoms seen in patients with depression/dementia, called face validity, 2) that the behavioral changes occurring in the animal can be objectively measured, called construct validity and 3) that the behavioral changes can be reversed by using the effective treatment in clinical. In particular, the study has shown OBX-induced enlargement of the lateral ventricles and down-regulation of vascular endothelial growth factor (VEGF) in the hippocampus, in addition to the decline in cholinergic system function, which are similarly progressive neurochemical features in Alzheimer's patients.

- The UCMS model has also met three main requirements of an effective depression model, including face validity, predictive value, and similarly in etiology and pathogenesis. In particular, based on classical methods, this study surveyed,

adjusted, and controlled experimental conditions such as: stressors, frequency efficiency, stress level, modeling time, and other relevant factors. Furthermore, the study suggested that the useful tools for behavioral assessment were the climb time in the forced swim test and the grooming behaviour in the open field test.

2. The effects of *Ocimum sanctum* L. and putative mechanisms underlying its actions

The thesis is the first publication to elucidate that *Ocimum sanctum* L. is a promising candidate for the prevention and treatment of not only cognitive deficits but also depressive disorders; the putative mechanisms underlying its actions are as follows:

- The ameliorative effects of *Ocimum sanctum* L. on cognitive deficits mediated by the enhancement of central cholinergic systems (reduced *ex vivo* activity of acetylcholinesterase in the brain and reversed the OBX-induced down-regulation of choline acetyltransferase (ChAT) expression levels), reduced the enlargement of the lateral ventricles, improved the suppression of hippocampal neurogenesis, reversed OBX-induced decrease in VEGF gene and protein expression levels.

- *Ocimum sanctum* L. attenuated the depression-like symptoms via enhancing monoaminergic systems including the noradrenergic, dopaminergic, and serotonergic systems.

Whereby, the mechanisms of reducing the enlargement of the lateral ventricles and increasing hippocampal neurogenesis were not only related to the anti-dementia effects but also had a close relationship with the antidepressant effect of OS. Evidence shows that hippocampal volume depletion, lateral ventricular enlargement, or local frontal lobe atrophy have been observed in depressed patients.

3. The chemical compounds play an important role in the effects of *Ocimum sanctum* L.

The thesis is the first document showing that the compounds in ethyl acetate fraction (OS-E) are responsible for the anti-dementia action, while the compounds in the n-butanol fraction (OS-B) are responsible for the antidepressant effects of OS extract. Specifically, ursolic acid and oleanolic acid, two major constituents in OS-E attenuated the OBX-induced cognitive deficits. Ursolic acid acts at relatively low

doses (6-12 mg/kg) by normalizing the function of central cholinergic systems and VEGF protein expression. Meanwhile, luteolin, apigenin, and apigenin-7-*O*-*β*-D-glucuronide in the n-butanol fraction are predicted to be the active constituents contributing an important role to the antidepressant effects.

Hanoi,   September, 2022

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