

**Multidisciplinary research in drug discovery: The importance of synergy amongst various fields of research in discovering the potential hits for atherosclerosis**

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**Abstract**

Current trend in research no longer focuses on one discipline alone. The establishment of quality multidisciplinary, borderless research programme is the way forward to ensure a bigger impact is produced either to scientific community or society at large. An obvious research programme that requires a significant multidisciplinary approach and collaborations from various fields of research is drug discovery. Institute of Marine Biotechnology (IMB) has embarked on a drug discovery programme to provide a scientific evidence on the marine natural resources used as traditional medicines in the treatment of illnesses with symptoms that represent atherosclerosis, based on the experience of society or prior ethno pharmacological knowledge practiced by indigenous people. This paper will discuss how various research disciplines of social science, natural product chemistry, natural product biology and molecular biology joined together and synergised to harness the experience-based traditional medicine towards the discovery of evidence-based compounds as potential hits for therapeutic intervention against the progression of atherosclerosis.

## Role of an antioxidants extracted from pacific oyster, *Crassostrea gigas*, in relieving stress and improving gonadal function in stressed female rats

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### [Background and Objective]

Many women daily experience excessive stress. The oxidative stress produced in the brain as a result of exposure to stress can excessively stimulate the hypothalamic-pituitary-adrenal (HPA) axis and suppress the hypothalamic-pituitary-gonadal (HPG) axis. In other words, hyperactivation of HPA axis disrupts hormone balance related to the estrus cycle, resulting in menstrual irregularities. To avoid this, intake of antioxidants that can reduce the oxidative stress in the brain is considered desirable.

Previously we isolated 3,5-dihydroxy-4-methoxybenzyl alcohol (DHMBA) as an antioxidant of the phenol family from the soft body of Pacific oyster (*Crassostrea gigas*) and confirmed penetrate of DHMBA into the rat brain and its effect in reducing the oxidative stress in the brain.

In the present study, we created a rat model of intracerebral oxidative stress and hyperactivation of HPA axis induced by exposure to stress. Using this model, we evaluated the effect of oral administration with the DHMBA-containing fraction of Pacific oyster soft body in reducing the oxidative stress in the brain and normalizing the excessively stimulated HPA axis. In addition, we examined whether oral administration with DHMBA alleviates the imbalance of menstruation-related hormones and the disrupted estrus cycle caused by stress.

### [Methods]

We used female Wister-Imaichi rats whose estrus cycle lasted for precisely 4 days. The 13-week-old rats allocated to the normal group (n = 10) were reared under non-stress condition. The rats of the same age allocated to the stress group (n = 10) and the DHMBA group (n = 10) were exposed for 26 days to the stress of isolated rearing and the stress of overcrowding, respectively. In the stress group, the rats were orally administrated with 0.5% methylcellulose while the DHMBA group rats were orally administrated with 0.5% methylcellulose containing DHMBA fraction. On Day 26, blood was sampled, and the hippocampus and the hypothalamus were removed from each rat. Levels of 8-OHdG (8-hydroxy-2'-deoxyguanosine), a marker of DNA oxidative injury, in the hippocampus were measured. Plasma levels of HPA axis hormones, i.e. corticotropin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH)

and corticosterone (Cort), were also measured. In addition, plasma levels of HPG axis hormones, i.e. follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and the hypothalamic corticotropin-releasing factor-receptor 1 (CRF-R1) were measured. The estrus cycle was assessed by vaginal smear.

[Results and Discussion]

When compared between the normal group and the stress group, the 8-OHdG level in the hippocampus was significantly higher and the plasma CRH and corticosterone levels were significantly higher in the stress group. These results suggest that oxidative stress was increased in the hippocampus and resulting in hyperactivation of the HPA axis.

Furthermore, plasma FSH and LH levels were lower in the stress group, indicating suppression of the HPG axis.

The 8-OHdG level in the hippocampus and the plasma CRH and corticosterone levels decreased significantly to normal levels in the DHMBA group when compared to the stress group. These results suggest that reactive oxygen species in the hippocampus was alleviated in the DHMBA group. As a result, the HPA axis was normalized. Furthermore, in the DHMBA group, plasma FSH and LH levels increased significantly to +the same level as the control group. Thus, treatment for anti-oxidant within the brain recovered the plasma levels of HPA axis hormones to normal levels, leading to a recovery in plasma levels of HPG axis hormones.

A normal estrus cycle was noted in 10 of the 10 rats from the normal group, 2 of the 10 rats from the stress group, and 5 of the 10 rats from the DHMBA group. As the HPA axis normalized, the estrus cycle tended to return to normal, although normalization of the estrus cycle was not seen in all rats.

[Conclusion]

In rats exposed to stress, the DHMBA fraction from Pacific oyster's soft body normalized the levels of HPA axis hormones, resulting in alleviation of stress and a tendency towards normalization of the hormone levels involved in the estrus cycle; however, complete normalization was not achieved.

**Keywords---** 3,5-dihydroxy-4-methoxybenzyl alcohol, stress, menstrual irregularities, antioxidant, HPA axis

## **Development of Antituberculosis Medicine from Indonesian Herbs**

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Indonesia is in the top five rank in the world based on the prevalence of tuberculosis. In general, tuberculosis is treated with drug combination following WHO guideline. Recently, there are big problem related to recurrence of tuberculosis in many patients due to the development of microbial resistance. To enhance the activity of standard anti-tuberculosis drug, we combine herbal medicine with standard drug.

In Indonesia, we have three types of herbal medicine namely *jamu*, standardized herbal and phytopharmaceutical product. In our study, phytopharmaceutical product for anti-tuberculosis were developed using ginger and noni as raw material. The two plants were used in folk medicine for treating cough, bloody cough, asthma and to increase immunity. This two plants were selected based on activity screening of 11 plants against *Mycobacterium tuberculosis*.

Anti-tuberculosis effect of ginger rhizomes extract as well as noni extract and its combination had been carried out *in vitro* against sensitive and resistant strain of *Mycobacterium tuberculosis*. Studies on toxicity of ginger rhizomes and noni extract combination had been carried out in rats followed by clinical trial in TB patients. Combination of ginger-noni extracts showed higher effects compared to each dose either in preclinical study and clinical study and showed to be safe. The combination enhances the antibacterial activity, shorten the time for conversion from positive acid-fast bacilli to negative acid fast bacilli in patients, it showed improvement of clinical outcomes and this combination is safe.

Soho Company has made collaboration with ITB in manufacturing and commercializing the result of this research with Fortibi as brand name.

**Key words:** antituberculosis, herbal medicine, phytopharmaceutical, ginger, noni