Summary of Doctoral Dissertation

Degree requested: Doctor of Life Science Applicant's name: Muhamad Aqmal Othman

Title of Doctoral Dissertation

Discovery of Natural Sphingomyelin Synthase Inhibitors against High Fat Diet-Induced Obesity and its Lipid Metabolism in Mice

（マウスにおける高脂肪食誘発肥満に対する天然スフィンゴミエリン合成酵素阻害剤の発見とその脂質代謝）

This study of ours focuses on identifying the sphingomyelin synthase (SMS) membrane protein inhibitors from the natural occurring sources. Thus, our group initiated a screening of more than 500 crude extracts libraries, to search for active medicinal plants which exhibits SMSs inhibitory activities. Based on the screening results, 5 plant extracts were identified with promising inhibition against target enzymes. Among them are *M. cinnamomea* and *Walsura pinnata* plants from Malaysia, *Chamaecyparis pisifera*, *Dryopteris crassirhizoma* and *Morus bombycis* plants from Hokkaido, Japan. Having said that, bioassay guided fractionation of the actives extracts resulted in the isolation of 13 natural SMS inhibitors.

Malabaricone C (**3**), an acylphenol isolated from the fruits of *M. cinnamomea*, has been identified as a lead natural sphingomyelin synthase inhibitor. Having the same mechanisms of action as the previously reported SMS knockout studies, malabaricone C was highly efficacious in preventing oleic acid uptake across the membrane which in turn reduced lipid droplet formation *in vitro*. Malabaricone C was also found to be able to reduce body weight gain, improve glucose tolerance and decrease lipid accumulation in the liver *in vivo*, thus making this the first report involving a plant derived SMS inhibitor against high fat diet-induced obesity. Its non-toxic nature makes malabaricone C a suitable candidate for its further development as a new drug or medicinal supplement to treat and prevent obesity.