（学位第３号様式）

学 位 論 文 要 旨

氏　名	PHAM THI BE TU
題　目	Pharmacological Effects of *Alpinia zerumbet*, *Momordica charantia* and Propolis Components ゲットウ、ゴーヤとプロポリスの構成成分の薬理学的作用

Obesity is becoming a global epidemic, and is the risk factor for hypertension, cancer, diabetes (type 2), aging, and cardiovascular complications. Okinawa, a southern island of Japan, was once known as one of top region of longevity in the world, boast an impressively low incidence of cardiovascular diseases, stroke, and cancer. However, the life expectancy at birth (LEB) for men in Okinawa is becomes now lower than that of national average, due to adopting a Western lifestyle. These problems give this research tremendous opportunity to explore and develop novel therapeutic ingredients for obesity and related diseases, leading to an extension of the healthy lifespan. Alpinia, bitter melon and propolis were chosen as a source of potential therapeutic materials, because these extracts contain a number of interesting bioactive constituents and possess health promoting properties as well as PAK1 inhibitory activity. PAK1 is the major oncogenic/aging kinase, which is responsible for many diseases. Thus, in this study, the effects of alpinia, bitter melon and propolis on anti-obesity, anti-aging and anti-melanogenic activities through the PAK1-blocking were investigated.

First of all, I found that hispidin, DK, and DDK isolated from alpinia had promising potential for anti-obesity. In particular, all the three compounds significantly increased intracellular cAMP, stimulated glycerol release, and inhibited lipid accumulation. Hispidin and DDK decreased intracellular triglyceride content and inhibited GPDH and pancreatic lipase activities with undesirable cytotoxicity toward 3T3-L1 cells. Furthermore, the effects of alpinia on anti-obesity and related diabetes (type 2) by inhibiting oxidative stress, ROS production and improving glucose uptake were clarified. On the other hand, because alpinia EOs showed strong anti-oxidant and anti-aging properties, and anti-melanogenic activities in B16F10 melanoma cells, it would be useful for anti-oxidant sources and skin whitening.

Secondly, I provided the first biochemical evidence for a specific role of PAK1 on melanin biosynthesis. The results revealed that silencing the endogenous PAK1 gene in mouse melanocytes through PAK1-specific shRNA significantly reduced melanin content and down-regulated intracellular tyrosinase activity. Thus, it would be a great interest to test if PAK1-blocking compounds from alpinia suppress the melanogenesis of skin cells. The results demonstrated that MTD, DK, labdadiene and hispidin reduced the melanin content and intracellular tyrosinase activity in the presence of melanogenesis stimulating hormones whose action depends on serum.

Finally, I confirmed that CBI, a major PAK1-blocking anti-cancer component of bitter melon as well as CAPE-based propolis called Bio30 from New Zealand and Propolin G-based Okinawa propolis completely inhibited the PAK1/serum-dependent melanogensesis of melanocytes, with only a marginal effect on their growth *per se*. Taken together, at least alpinia, bitter melon and propolis appears to be among effective sources for both controlling and preventing obesity, diabetes, and melanogenesis. The findings of PAK1/dependent melanogenesis could be a quick and inexpensive screening system for potent synthetic or herbal PAK1-blockers which are useful for clinical/cosmetic application such as cancer therapy and skin-whitening.