(学位第３号様式)

学 位 論 文 要 旨

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題　目	Utilization of Okinawa Plants for Pesticidal and Medicinal Applicabilities (殺虫及び医薬への応用を目的とした沖縄産植物の利用)

Bioactive compounds from plants have been recognized as an important source for lead discovery in medicine as well as in agrochemical in recent years. However, only a few identified components are used directly as active ingredient in crop protection and medicine due to mainly low biological potency. This drawback gives the opportunity and inspiration for design and development of novel compounds with improved bioactivities. Alpinia, leucaena, pilosa, and bitter melon are popular plants in Okinawa, and contain the interesting bioactive constituents such as DK, DDK, mimosine, and cucurbitacin I. These compounds have been known as promising structural units in the field of medicinal and agricultural chemistry. Therefore, in this study, novel biological properties of four above isolated compounds were explored in order to develop more potent derivatives for pesticidal activities, and for PAK1 blocking, anticancer, skin-brightening, and hair loss treatment as well.

Firstly, I found that mimosine phosphoramidothionate derivatives had promising potential effects as insecticide and nematicide. Their activities were 30-100 times more active than those of starting material mimosine. Furthermore, a small library of ten mimosine dipeptides, mimosinol, and deuterated mimosinol (D-mimosinol) were effective melanogenesis inhibitors in B16F10 melanoma cells by suppressing the cellular tyrosinase without undesirable cytotoxicity. Thus, it could be used as potential compounds in skin brightening. In addition, mimosine dipeptides also inhibited strongly cyclooxygenases (COX-1/2) which are major targets for anti-inflammatory drugs. More interestingly, mimosinol and D-mimosinol showed an outstanding activity for hair cell growth promotion; therefore, it would also be useful for hair loss treatment.

Secondly, since PAK1 is essential for a variety of diseases, the search for effective PAK1 inhibitors is at the center of very competitive efforts. I introduced a new method coined “Macaroni-Western” assay, by combination of immunoprecipitation (IP) of PAK1 from cell lysates and in vitro kinase assay based on ATP-dependent luciferin-luciferase system, for the assessment of potent and safe PAK1 blockers in cell culture. This universal system allowed to monitor any change in the kinase activity of PAK1 in cells directly, independent of its auto-phosphorylation sites, without SDS-PAGE. I also displayed new findings that DDK, DK, hispidin, and cucurbitacin I directly inhibited PAK1 in vitro. Three hispidin derivatives inhibited PAK1 at a low micromolar level. Interestingly, mimosine tetrapeptides such as MFFY and MFWY suppressed PAK1 at a nanomolar level, and thus could be used as drug candidates for treatment of various diseases in the future. In particular, PAK1 is responsible for the growth of cancer, melanogenesis, and hair loss. Based on the results, some of the above PAK1 blockers, in particular cucurbitacin I, could be a good candidate for treatment of these diseases.

In conclusion, this study demonstrated that DK, DDK, mimosine, and cucurbitacin I are potential leads for the development of more potent novel drugs and pesticides. The highlight I found was several herbal compounds from Okinawa plants were effective PAK1 blockers which were good candidates for the treatment of cancer, hair loss, and skin brightening. Moreover, new “Macaroni-Western” PAK1 assay system I developed, make advantages to select only highly cell-permeable PAK1 blockers useful for potential clinical application.