

Bioactive Compounds Derived from Hibiscus sabdariffa and Vanilla pompona: The Therapeutic Intervention Potential and Molecular Mechanisms for Skin Disorders

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Title : Bioactive Compounds Derived from *Hibiscus sabdariffa* and *Vanilla pompona*:
The Therapeutic Intervention Potential and Molecular Mechanisms for
Skin Disorders
(*Hibiscus sabdariffa* 及び *Vanilla pompona* 由来の生理活性物質：皮膚疾患治療
に対しての可能性ならびに活性発現メカニズムの解明)

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Thesis Summary

In this thesis, two plants cultivated in the Kyushu region of Japan as the study objective, namely *Hibiscus sabdariffa* L. (Malvaceae) and *Vanilla pompona* Schiede (Orchidaceae). Both plants have high-quality value and are extensively utilized in the food industry. Nonetheless, their potential applications in pharmaceuticals and cosmeceuticals development remain unexplored. Accordingly, this study aimed to explore their therapeutic intervention potential against skin disorder as well as unravel their underlying mechanisms. By employing a combination of analytical chemistry for secondary metabolites, column chromatography technique and bio-guided isolation approach, as well as establishing various evaluation systems based on cell biology, this study validated several bio-active compounds from *H. sabdariffa* and *V. pompona* and clarified their possible mechanisms according to molecular biology.

In the first chapter of this thesis, the biological activities of the crude extracts, chromatographic fractions, and hibiscus acid isolated from *H. sabdariffa* calyxes were evaluated for their potential bioactivities. Their ability to promote extracellular matrix synthesis in skin fibroblasts was evaluated by enzyme-linked immunosorbent assays. Their anti-inflammatory activity was evaluated in a nitric oxide (NO)-Griess inflammatory experiment. Furthermore, hibiscus acid was found to have a strong anti-oxidative stress effect through the establishment of an oxidative stress model induced by hydrogen peroxide. Several assays indicated that hibiscus acid treatment can effectively reduce extracellular adenosine triphosphate (ATP) secretion and carbonyl protein production, as well as maintain a high level of reduced/oxidized glutathione (GSH/GSSG) in skin cells, thus providing a possible mechanism by which hibiscus acid can counter antioxidative stress.

Regarding the second chapter of this thesis, two phenolic glycosides were isolated for the first time from *V. pompona*: bis [4-(β -D-O-glucopyranosyloxy)-benzyl] (S)-2-isopropylmalate (Compound 1) and bis [4-(β -D-O-glucopyranosyloxy)-benzyl] (2R,3S)-2-isopropyltartrate (Compound 2). We have discovered that the crude extract of *V. pompona* leaves and stems and its two phenolic glycosides (compounds 1-2) are highly effective in reversing skin senescence. *V. pompona* and compounds 1-2 were found to promote the synthesis of collagen, hyaluronic acid, and elastin in skin fibroblasts in a normal skin cell model; in a replicative senescence model, *V. pompona* and compounds 1-2 significantly reduced the ageing phenotype in skin fibroblasts. These compounds

also demonstrated a significant protective effect in a UV-induced photo-senescence model; the possible mechanisms of this effect were further investigated in this study. This study is the first to develop *V. pompona* leaves and stems as new sources of bioactive compounds and to examine their therapeutic potential for skin senescence. (**Figure 1**)

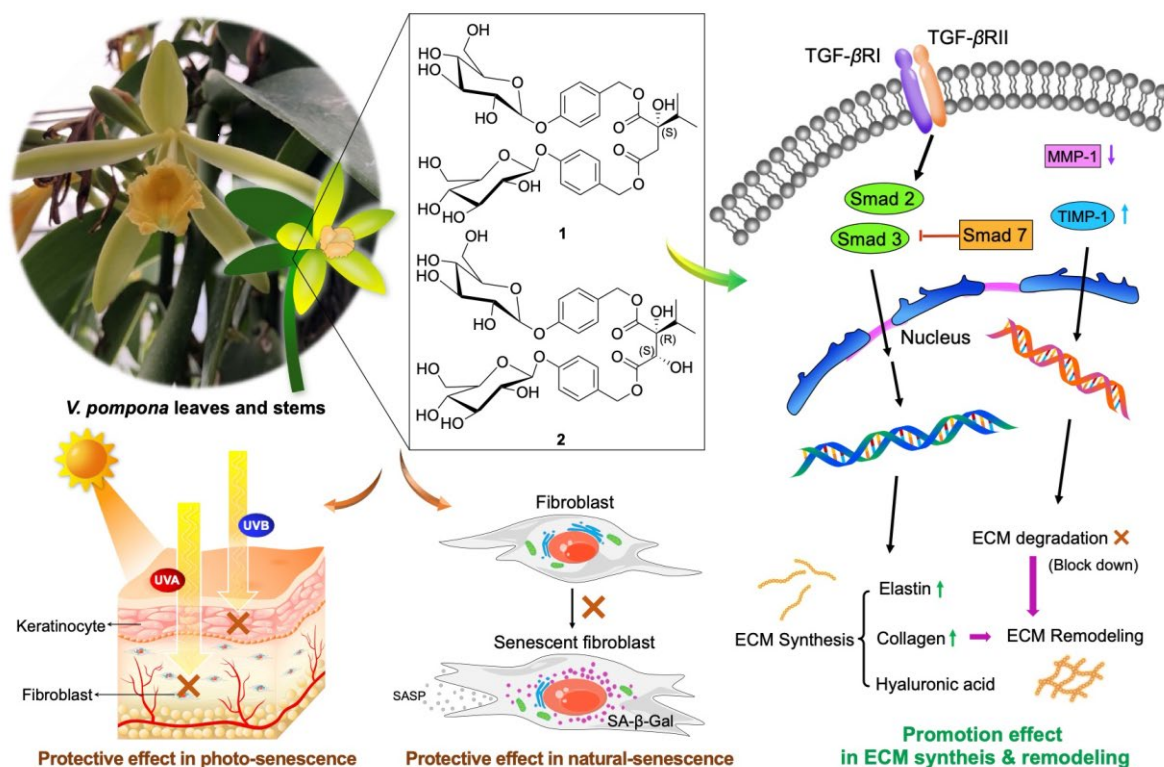


Figure 1. Abstract graphic for the second chapter of study : two phenolic glycosides (compounds 1-2) from *V. pompona* and their biological potential against skin senescence

Moreover, we were surprised to find that compounds **1-2** had the ability to stimulate melanogenesis in both mouse melanoma cells and human melanoma cells at the low concentrations. After the further confirmation, we found that compounds **1-2** could also significantly enhance the tyrosinase activity in these two melanoma cells, additionally could change the cell morphology and accumulate melanin granules on cell dendrites. These findings indicated that compounds **1-2** at the low concentrations may affect the synthesis and transport of melanin in melanoma cells, which could be used as a potential natural product to alleviate hypopigmentation diseases. The further exploration of its underlying mechanism regarding this phenomenon is under working.

The present study is the first to develop these two plants as new sources of bioactive compounds and to evaluate their therapeutic potential against skin disorder, provided a new way as well as the scientific basis for the utilization of *H. sabdariffa* and *V. pompona* as raw materials for potential pharmaceutical or cosmeceutical applications. Meanwhile, the natural product development approaches used in this study can efficiently search for the major bio-active secondary metabolites from plants, and the established biological activity evaluation system is also provided a good idea for developing natural product in treatment of skin senescence as well as skin hypopigmentation diseases.