

学位論文の要旨 (論文の内容の要旨)  
Summary of the Dissertation (Summary of Dissertation Contents)

論 文 題 目

Dissertation title

Anti-Blood Cancer Activities of Bioactive Compounds from Rice (*Oryza sativa* var. Koshihikari) and an Invasive Weed (*Andropogon virginicus*)

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### 1. Background

Blood cancer (1.2 million cases per year) has been a serious human disease during a long history with a high mortality rate (58%). Therefore, this study was conducted to investigate promising candidates from plants for inhibiting blood cancer. Among plant sources, *Andropogon virginicus* is an invasive weed that distributes globally, threatening agriculture and economics in many countries. Thus, research on pharmaceutical properties may lead to further strategies to take advantage of this serious invasive weed that was once thought to be of no use. On the other hand, rice (*Oryza sativa*) is an important food crop in the world, which has been recently being received increasing attention for the research on medicinal purposes. In rice, momilactones are high valuable diterpene lactones exhibiting multiple biological benefits. Based on these reasons, we aimed (1) to explore potential phytochemicals and pharmaceutical properties of the invasive weed *A. virginicus* with focus on antioxidant, anti-skin aging, anti-diabetic, and anti-blood cancer properties and (2) to determine the potentials of momilactones isolated from rice (*O. sativa* var. Koshihikari) for preventing blood cancer.

### 2. Structure of dissertation

Chapter 1. General introduction

Chapter 2. Pharmaceutical properties of an invasive weed *Andropogon virginicus*

Chapter 3. Cytotoxic activities of momilactones against leukemia, lymphoma, and multiple myeloma cell lines

Chapter 4. Cytotoxic mechanism of momilactones against acute promyelocytic leukemia and multiple myeloma cell lines

Chapter 5. Effects of *in vitro* digestion on anti-blood cancer properties of momilactones

Chapter 6. General discussion

### 3. Materials and methods

#### *Materials*

*A. virginicus*' aerial plant parts were extracted by Soxhlet extraction method, followed by liquid-liquid phase extraction to obtain total crude (T-Anvi), hexane (H-Anvi), ethyl acetate, (E-Anvi), butanol (B-Anvi), and water (W-Anvi) extracts.

Momilactones were isolated and purified from the laboratory of Plant Physiology and Biochemistry, Hiroshima University, Japan (Quan et al., 2019b).

#### *Biological activity*

Antioxidant activities of samples were determined via antiradical (DPPH and ABTS), reducing power,  $\beta$ -carotene bleaching assays (Quan et al., 2019).

Enzymatic assays including tyrosinase and  $\alpha$ -amylase inhibitory effects of *A. virginicus*' extracts were evaluated following the method presented by Quan et al. (2019).

Anticancer assays consisting of MTT, annexin V apoptosis, cell cycle, and western blotting were conducted to screen the anticancer properties of momilactones. The corresponding cell lines for blood cancer were included leukemia (HL60, Meg-01, and K562), lymphoma (Mino), and myeloma (KMS-11 and U266). Besides, a non-cancerous cell line namely MeT-5A was used in this study.

#### ***In vitro* digestion model**

The effects of *in vitro* digestion on the bioaccessibility and cytotoxic activities of momilactones against blood cancer cell lines were investigated following the method described by Un et al. (2022).

#### ***Phytochemical analysis***

The chemical analyses were conducted applying spectrophotometer, gas chromatography-mass spectrometry (GC-MS), and liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) methods.

### **4. Results and discussion**

In Chapter 2, we indicate that the invasive weed *A. virginicus* may be a promising source of antioxidants, anti- $\alpha$ -amylase, and anti-tyrosinase abilities, and cytotoxicity against chronic myeloid leukemia cell lines. Besides, *A. virginicus* aerial parts are rich in flavonoids, palmitic acid, phytol, and  $\gamma$ -sitosterol, which may play a vital role in the biological activities of the respective extracts.

From Chapter 3, we highlight that MB and MAB can inhibit various blood cancer cell lines including leukemia, lymphoma, and multiple myeloma by inducing cell apoptosis. Notably, the cytotoxicity of MB and MAB is close to the well-known drugs of Doxorubicin in inhibiting Meg-01 and K562. Meanwhile these compounds are stronger than the widely applied medicines of Doxorubicin and Ibrutinib in suppressing HL-60 and U266, respectively. Whereas these compounds display an insignificant effect on non-cancerous cells.

In Chapter 4, MB and MAB at 5  $\mu$ M promote acute promyelocytic leukemia (HL-60) and multiple myeloma (U266) cell apoptosis by activating the phosphorylation of p-38 in the mitogen-activated protein kinase (MAPK) pathway and regulating the relevant proteins (BCL-2 and caspase-3) in the mitochondrial pathway. Besides, these compounds may induce G2 phase arrest in HL-60 cell cycle through the activation of p-38 and disruption of CDK1 and cyclin B1 complex. Meanwhile MB and MAB show insignificant effects on cell apoptosis and cell cycle of non-cancerous cell line MeT-5A.

For Chapter 5, the finding shows that the bioaccessibility and cytotoxicity of momilactones significantly reduce through the digestive stages including oral, gastric, and intestinal phases.

A general discussion is presented in Chapter 6. Particularly, this is the first study to highlight that *A. virginicus* may be a promising source of antioxidant, anti-diabetic, anti-skin aging, and anti-blood cancer agents. In addition, momilactones isolated from rice (*O. sativa* var. Koshihikari) husks can inhibit blood cancer cell lines by regulating the proteins related to apoptosis and cell cycle pathways. However, cytotoxic activities of momilactones may be significantly decreased during digestion. Therefore, forthcoming studies should be conducted to improve the bioaccessibility of momilactones, followed by *in vivo* and clinical tests to confirm their capacity to develop novel anti-blood cancer drugs. In another aspect, the combination of momilactones from rice and isolated components from *A. virginicus* may be a potential approach for developing blood cancer treatments, especially for patients complicated with other health problems such as oxidative stress and chronic disorders.

備考 論文の要旨はA4判用紙を使用し、4,000字以内とする。ただし、英文の場合は1,500語以内とする。

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