



# HOKKAIDO UNIVERSITY

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| Title               | Study on Malabaricone C Isolated From the Mace of <i>Myristica fragrans</i> as Natural Antiviral Against SARS-CoV-2 and Discovery of Its Mechanism of Actions [an abstract of dissertation and a summary of dissertation review] |
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## Abstract of Doctoral Dissertation

Degree requested Doctor of Life Science Applicant's name MUTMAINAH

### Title of Doctoral Dissertation

Study on Malabaricone C Isolated From the Mace of *Myristica fragrans* as Natural Antiviral Against SARS-CoV-2 and Discovery of Its Mechanism of Actions

(香辛料由来マラバリコーンCによる SARS-CoV-2 感染阻害とその機構解明)

SARS-CoV-2, or Severe Acute Respiratory Syndrome-Coronavirus-2, is an enveloped beta coronavirus responsible for a global health crisis. The disease it causes, COVID-19, manifests respiratory symptoms such as cough, fever, and severe pneumonia, which can result in death. Similar to its predecessor, SARS-CoV-1, which occurred two decades earlier, this novel coronavirus invades human cells by attaching its spike protein to Angiotensin-Converting Enzyme-2 (ACE2) receptors. However, while SARS-CoV-1 uses endocytosis to enter host cells, SARS-CoV-2 favors a route through transmembrane serine protease 2 (TMPRSS2)-mediated membrane fusion. Although new vaccines and antiviral drugs have been created to combat SARS-CoV-2, the need for additional COVID-19 treatments remains due to limited options. From a safety perspective, bioactive compounds sourced from foods and edible plants present both potential and challenges as new therapeutic agents against SARS-CoV-2. This study highlights the efficacy of malabaricone C, a naturally occurring compound, along with its synthetic derivatives, in inhibiting SARS-CoV-2 infection. The first chapter introduces SARS-CoV-2 and recent treatment advancements, including a review of natural antiviral agents and their mechanisms for inhibiting infections.

The second chapter centers on malabaricone C, a compound derived from edible plants like nutmeg, identifying it as a novel natural inhibitor of SARS-CoV-2. Malabaricone C and its derivatives demonstrated an EC<sub>50</sub> range of 1–1.5  $\mu$ M against SARS-CoV-2 and its variants in mammalian cells, indicating its potential as a safe therapeutic candidate for treating and preventing COVID-19. Additionally, the chapter will present a novel method for visualizing virus-assisted cell fusion.

In the third chapter, various possible mechanisms by which malabaricone C inhibits SARS-CoV-2 infection in vitro are explored. Potential targets include blocking the SMS enzyme, disrupting the interaction between Spike RBD and ACE2, inhibiting TMPRSS2, and interfering with lipid raft assembly on the cell membrane. This study suggests that malabaricone C inhibits SARS-CoV-2 entry primarily by affecting lipid raft assembly in the host cell membrane.