

博士論文の内容の要旨

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論文題目	Study on the screening of neuroprotective compounds from agricultural products using a <i>Caenorhabditis elegans</i> model (線虫モデルを用いた農業生産物からの神経保護物質の探索に関する研究)

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The longevity and neuroprotective effects of dry green tomato and *Glochidion littorale* extract on *Caenorhabditis elegans* were investigated in this doctoral dissertation.

In Chapter 1, a literature review is included, and the objectives of this thesis are highlighted. Aging is considered to affect various molecular pathways and is a risk factor for neurodegenerative pathologies, such as Alzheimer's disease and Parkinson's disease. Oxidative stress is one of the main pathways leading to aging and age-related diseases. Compounds that exhibit strong antioxidant properties seem to be efficient countermeasures against oxidative stress. Hence, plants rich in antioxidant molecules are considered important.

The Maillard reaction, which is a reaction between amino acids or proteins and reducing sugars in the presence of heat, occurs every day with or without human intervention. The reaction leads to the formation of browning compounds, flavor, and Maillard reaction products (MRPs). Some MRPs have been reported to have strong antioxidant properties, but their neuroprotective effects have yet to be explored. As tomato is produced and consumed worldwide, dried tomatoes might be a good source of MRPs. In addition, numerous plants used in traditional medicine in Southeast Asian countries are considered beneficial for health. Several species from the genus *Glochidion* have been investigated for their rich flavonoid content. *Glochidion littorale* leaves are used as folk medicine against general injuries and diseases in countries such as Thailand. However, there are few reports concerning their neuroprotective effects.

Chapter 2 investigates the anti-aging and neuroprotective effects of MRP fractions derived from dried tomatoes (*Solanum lycopersicum* L.). *Caenorhabditis elegans* was used as an in vivo model. The results showed that the MRP fraction has a strong radical scavenging activity, as evaluated through DPPH and ABTS assays. Aqueous extracts of green tomatoes and their MRP fractions showed a significant lifespan extension effect in *C. elegans*. Furthermore, the MRP fraction protected worms against H₂O₂ damage and MPP⁺-induced neurotoxicity in *C. elegans*.

In Chapter 3, the neuroprotective effect of *Glochidion littorale* leaf extract (GLE) on *C. elegans* and the probable mechanisms involved are investigated. Specifically, the antioxidant activity of GLE was evaluated in vivo by inducing oxidative stress in worms and by measuring the intracellular reactive oxygen species (ROS) using a fluorescent probe (2',7'-dichlorodihydrofluorescein-diacetate). Compared with the control, the GLE-treated worms showed significantly reduced ROS intensity and increased oxidative stress resistance. Thereafter, the neuroprotective effects were evaluated in wild-type *C. elegans* and transgenic mutant (*daf-2* and *daf-16* mutant) worms. The results showed a neuroprotective effect of GLE and the possible involvement of the DAF-16 transcription factor in both stress resistance and the neuroprotection pathway.

Finally, Chapter 4 provides a summary and conclusion of the study. The findings suggest that the MRP fraction from dry green tomatoes exerts possible lifespan extension and neuroprotective effects on *C. elegans*. Second, the results suggest an oxidative stress resistance and possible neuroprotective effects of GLE in *C. elegans* via activation and translocation of the transcription factor DAF-16 in the nucleus. These agricultural products may be a promising preventative strategy for age-related cognitive decline in the elderly.