学位第３号様式）

# 学 位 論 文 要 旨

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| 題　目 | Study on the functionality and safety of areca nut (*Areca catechu* L.), a chewing food<br>咀嚼嗜好品である檳榔子の機能性と安全性に関する研究 |


Areca nut (*Areca catechu* L.) is a tropical plant widely cultivating in Southeast Asia, and traditionally used as a chewing food. Previous studies revealed that areca nut exhibited different bioactivities since areca nut contains two kinds of bioactive components, polyphenols and alkaloids. To determine which of the areca nut's components contributes to areca nut biofunctions, we prepared whole areca nut extract (ANE), areca nut polyphenol (ANP), and arecoline (ARE), as research materials in this study, and then investigated the functionality and safety of areca nut and its different components through *in vivo* and *in vitro* experiments.

Firstly, the antioxidant activity of ANP was explored in lipopolysaccharides (LPS)-stimulated mouse RAW264.7 cells. The results revealed that ANP reduced the level of LPS-induced reactive oxygen species (ROS) and enhanced the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1). RNA-seq analysis showed that ANP down-regulated the transcription of genes related to the cancer pathway at 160 μg/mL, the inflammatory pathway as well as viral infection pathway at 320 μg/mL. Collectively, these results showed that ANP activated the Nrf2/HO-1 antioxidant pathway to reduce ROS level induced by LPS.

Next, the effects and molecular mechanisms of areca nut and its major ingredients on the prevention of dyslipidemia was assessed by a Western diet-induced mouse dyslipidemia model. Male C57BL/6N mice were divided into five groups and fed with a normal diet (ND), Western diet (WD), WD with ANE, ANP or ARE for 12 weeks. The results revealed that ANP significantly reduced WD-induced body weight, liver weight, epididymal fat weight, and liver total lipid rate. Serum biomarkers showed that ANP ameliorated WD-enhanced serum concentrations of total cholesterol and non-highdensity lipoprotein (non-HDL). Moreover, analysis of cellular signaling pathways on lipid metabolism revealed that the expressions of sterol regulatory element-binding protein 2 (SREBP2) and 3-hydroxy-3-methylglutaryld coenzyme A reductase (HMGCR) were significantly downregulated by ANP. Furthermore, the results of gut microbiota analysis revealed that ANP increased the relative abundance of beneficial bacterium *Akkermansias* and decreased the relative abundance of pathogenic bacterium *Ruminococcus* while ARE showed the opposite results to ANP.

In conclusion, areca nut polyphenols possessed antioxidant and anti-inflammatory effects by activating the Nrf2/HO-1 antioxidant pathways Moreover, areca nut polyphenols ameliorated WD-induced dyslipidemia by increasing the abundance of beneficial bacteria in the gut microbiota and reducing the expressions of SREBP2 and HMGCR. while areca nut ARE inhibited this improvement potential. These results provide a scientific basis to understand the functionality and safety of areca nut polyphenols and arecolines, and will give new insights to develop new functional products of areca nut with safety.