（学位第３号様式）

学 位 論 文 要 旨

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題　目	The anti-inflammatory activities and molecular mechanisms of *Lonicera caerulea* L. berry （ハスカップベリーの抗炎症活性及び分子機構に関する研究）

Lonicera caerulea L., is a member of the Caprifoliaceae family that grows naturally in the cool Northern Hemisphere. Its berry is rich in polyphenols, and recently receiving attention in the prevention against chronic diseases due to its potential antioxidant and anti-inflammatory properties. However, the molecular mechanisms underlying the activities remain unclear. Thus, the present study aimed to investigate the protective effects and molecular mechanisms of *Lonicera caerulea* L. berry polyphenols (LCBP) against excessive inflammation and relevant diseases, using both cell and animal models.

First, *in vitro* anti-inflammatory effects and molecular mechanisms of LCBP were investigated in lipopoly-saccharide (LPS)-activated RAW264.7 cell model. Pretreatment with LCBP concentration-dependently suppressed the production of inflammatory mediators including IL-1β, IL-6, TNF-α, nitric oxide (NO), and PGE_2. Cell signaling analysis revealed that LCBP down-regulated TAK1-mediated MAPK and NF-κB pathways. Moreover, LCBP reduced oxidative stress by up-regulating the expression of Nrf2 and MnSOD. Finally, cyanidin 3-glucoside (C3G) and -(-)epicatechin (EC) were identified to be the major bioactive components of LCBP for these activities. These data demonstrated that LCBP rich in C3G and EC attenuated LPS-induced inflammation by down-regulating TAK1-mediated MAPK and NF-κB pathways, and up-regulating the expression of Nrf2 and MnSOD.

Second, *in vivo* anti-inflammatory effects of LCBP were investigated in a LPS-induced mouse paw edema model. Oral administration with LCBP attenuated paw edema and significantly decreased the serum cytokines levels including IL-1β, IL-2, IL-3, IL-4, IL-6, IL-10, IL-12 (p70), KC, MCP-1, MIP-1α, RANTES and TNF-α in LPS-induced mice, but had no significant effects on IL-1α, IL-9, IL-12(p40), IL-13, G-CSF, GM-CSF, IFN-γ and MIP-1β. The data demonstrated that oral administration with LCBP attenuated LPS-induced inflammation by inhibiting the production of multiple proinflammatory cytokines, rather than promoting the production of anti-inflammatory cytokines.

Third, the preventive effects of LCBP against chronic inflammation-related diseases were investigated in adjuvant-induced arthritis (AIA) rat model. Oral administration of LCBP attenuated AIA rat symptom. The serum levels of pro-inflammatory factors including TNF-α, IL-1β, IL-6, and NO were significantly reduced in LCBP-fed rat. The production of inflammatory enzymes, iNOS and COX-2, in the spleen was also significantly reduced. Moreover, serum transaminases including GOT, GPT and GGT were decreased, and the antioxidant enzymes including SOD and GPx were restored. Thus, LCBP attenuated rat AIA symptom by both decreasing the production of proinflammatory factors and enhancing the activity of antioxidant enzymes.

Finally, the crosstalk between the antioxidant and anti-inflammatory activities of LCBP was investigated in an experimental model of nonalcoholic steatohepatitis (NASH), which is a common disease that closely associated with inflammation and oxidative stress. Oral administration of LCBP improved histopathological features of NASH with higher insulin sensitivity, less lipid peroxidation, and lower levels of cytokines. Moreover, LCBP increased the expression of Nrf2 and MnSOD, but decreased the expression of FoxO1 and HO-1. These data revealed that LCBP could attenuate NASH by both enhancing the expression of antioxidant proteins and inhibiting the production of oxidative stress-related proteins.

In summary, LCBP rich in C3G and EC exerted the protective effects against chronic inflammation-related diseases by suppressing the production of multiple proinflammatory mediators and oxidative stress factors. Molecular data revealed that LCBP inhibited inflammation by down-regulating TAK1-mediated MAPK and NF-κB pathways, and up-regulating the expression of Nrf2 and MnSOD. These results provide an insight into understanding the anti-inflammatory effects and molecular mechanisms of *Lonicera caerulea* L. berry.