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Mitigating effects of *Euphorbia hypericifolia* on citrinin-triggered ferroptosis and epithelial barrier dysfunction

임승준

경북대학교 축산BT학과 동물영양유전체학 실험실

Citrinin (CTN) is a mycotoxin frequently detected in contaminated food and feed and is known to impair intestinal barrier integrity by inducing oxidative stress and cytotoxicity. While several mycotoxins have been implicated in ferroptosis-an iron-dependent form of regulated cell death-the involvement of CTN in this pathway remains unclear. This study aimed to determine whether CTN induces ferroptosis in intestinal epithelial cells and to evaluate the protective effects of *Euphorbia hypericifolia* (EH) against CTN-induced oxidative damage and tight junction (TJ) disruption. IPEC-J2 cells were treated with CTN, and intracellular ferrous ion (Fe^{2+}) accumulation, reactive oxygen species (ROS) levels, and TJ integrity were assessed using FerroOrange staining, DCFH-DA fluorescence, RT-qPCR, immunofluorescence, and WST-1 assays. A high-throughput screen of 459 natural compounds identified EH as a potent candidate for mitigating CTN toxicity. CTN exposure significantly increased intracellular Fe^{2+} and ROS levels, suppressed antioxidant gene expression (particularly CAT), and disrupted ZO-1 expression and TJ structure-features consistent with ferroptosis-like cell death. Co-treatment with EH reversed these effects by restoring antioxidant gene expression, reducing oxidative and iron stress, and maintaining TJ morphology. Phytochemical profiling of EH revealed multiple bioactive constituents potentially responsible for its protective activity. These findings suggest that CTN induces ferroptosis-like cytotoxicity in IPEC-J2 cells, and that EH exerts a protective effect by modulating redox balance and iron metabolism, supporting its potential application as a natural feed additive for maintaining intestinal barrier function.

Key words : citrinin, ferroptosis, *Euphorbia hypericifolia*, IPEC-J2, oxidative stress, tight junction, natural product