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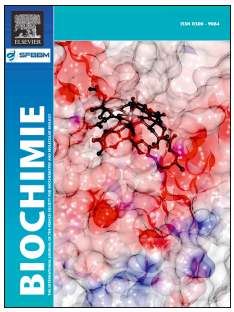


Upregulation of aquaporin 3 expression by diterpenoids in *Euphorbia pekinensis* is associated with activation of the NF-κB signaling pathway in the co-culture system of HT-29 and RAW 264.7 cells

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# Upregulation of aquaporin 3 expression by diterpenoids in *Euphorbia pekinensis* is associated with activation of the NF-κB signaling pathway in the co-culture system of HT-29 and RAW 264.7 cells

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**Abstract:** This study was designed to evaluate the toxic effects of diterpenoids separated from the roots of *Euphorbia pekinensis*, a type of widely used traditional Chinese medicine. This herb has intestinal toxicity associated with its complex diterpenoids. In this study, the diterpenoids (pekinenin A, pekinenin C, pekinenin F, pekinenin G, yuexiandajisu A, (-)-(1S)-15-hydroxy-18-carboxycembrene) elevated the expression of interleukin 1 beta and tumor necrosis factor alpha in a dose-dependent manner at doses of 6.25, 12.5, and 25 μM in RAW264.7 monocultures. Pekinenin C increased the expression of phosphorylated IκB and phosphorylated p65 in RAW264.7 monocultures, indicating that it stimulated a substantial inflammatory response and activated the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. A co-culture model of RAW 264.7 mouse macrophage cells and HT-29 human intestinal epithelial cells was established to study the correlation between inflammation and aquaporin (AQP) expression and to evaluate the toxicity of different diterpenoids from *E. pekinensis.* Pekinenin C (6.25, 12.5, and 25 μM) increased AQP3 mRNA and protein expression of HT-29 cells in the co-culture system in a dose-dependent manner but not in HT-29 monocultures. AQP3 mRNA and protein expression peaked at 2 and 3 h of HT-29 cells in the co-culture system, respectively. In contrast, their expression peaked more slowly in the monoculture system. After the specific NF-κB inhibitor BAY11-7082 (5, 10, and 20 μM) was added to the co-culture system, the release of cytokines and increased AQP3 expression caused by pekinenin C were inhibited. Comparisons of the representative monomeric compound pekinenin C, diterpenoid monomer mixtures, and total diterpenoids from *E. pekinensis* showed that the monomer mixtures had the most toxicity. In conclusion, this study demonstrated that *E. pekinensis* induces inflammation and increases the expression of AQP3, causing disorders of water metabolism, which may lead to gastrointestinal side effects such as diarrhea.

**Keywords:** *Euphorbia pekinensis*; diterpenoids; aquaporins; laxative effect; intestinal inflammation; Jing Da Ji

## 1. Introduction

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