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Stromal interacting molecule 1 (Stim1) plays important roles in regulating store-operated Ca2+ entry (SOCE), and controls invasion by cancer cells. However, the mechanisms and functions of Stim1 in glioma progression are still unclear. In this study, we investigated the effects of targeting Stim1 expression on glioma cell invasion. By analyzing profiles of GBM patients from RNA-sequencing data in The Cancer Genome Atlas (TCGA), higher expression levels of STIM1 were correlated with the poor survival. Furthermore, signaling pathways associated with tumor malignancy, including the epithelial-to-mesenchymal transition (EMT), were activated in patients with high STIM1 expression according to gene set enrichment analyses. Higher Stim1 levels were found in glioma cells compared to human astrocytes, and these higher levels enhanced glioma cell invasion. Xanthohumol (XN), a prenylated flavonoid extracted from the hop plant Humulus lupulus L. (Cannabaceae), significantly reduced cell invasion through inhibiting Stim1 expression. From an micro(mi)RNA array analysis, miR-4725-3p was upregulated by XN treatment. Overexpression of miR-4725-3p inhibited glioma cell invasion via directly targeting the 3'-untranslated region of STIM1. The extracellular signal-regulated kinase/c-Fos pathway was also validated to participate in XN-upregulated miR-4725-3p expression according to promoter and chromatin immunoprecipitation assays. These results emphasize that miR-4725-3p-inhibited STIM1 signaling is involved in XN-attenuated glioma cell invasion. These findings may provide insights into novel therapeutic strategies for future glioblastoma therapy and drug development.