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Tiliroside Produced Anti-Neuroinflammatory Effects Through Interference With NF-κB And MAPK Signalling In LPS+ IFN-γ Stimulated BV-2 Microglia.

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Tiliroside is a glycosidic flavonoid, which possesses anti-inflammatory, antioxidant, anticarcinogenic and hepatoprotective activities. It is contained in several dietary plants like linden, rosehip, raspberry and strawberry [1, 2]. In this study the effects of tiliroside on the production of prostaglandin E_2 (PGE_2) and nitric oxide (NO) from LPS+ IFN-γ stimulated BV-2 microglia as well as its interference with NF-κB and MAP kinase signaling cascades were investigated.BV-2 cells were stimulated with LPS (100ng/ml) and IFN-γ (5ng/ml) in the presence or absence of tiliroside (2-6μM). After 24 hours, supernatants were collected to measure PGE_2 and NO production. MTT assay was used to determine the effect of tiliroside on BV-2 microglia viability. Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) protein expressions were evaluated in LPS+ IFN-γ activated BV-2 microglia by western blot. NF-κB transcriptional activity was evaluated using the luciferase reporter gene assay. Protein expressions of phosphorylated IκB, IKK, p38 and MAPKAPK2 in the presence or absence of tiliroside were evaluated using western blots after one hour stimulation with LPS (100ng/ml) and IFN-γ (5ng/ml). Tiliroside (2-6μM) dose dependently ($p<0.05$) inhibited PGE_2 and NO production without effecting viability of BV-2 cells. Tiliroside (6μM) caused a significant ($p<0.05$) inhibition of COX-2 expression by 27±4.3% and iNOS protein expression by 60.3±1.2% compared to LPS+ IFN-γ control. Further experiments revealed significant ($p<0.05$) inhibition of nuclear translocation of activated NF-κB by 26.3±3.1% with 6μM tiliroside. The compound (6μM) produced significant ($p<0.05$) inhibition of IκB and IKK phosphorylation by 51.9±3% and 54.9±4.1%. At 6μM, tiliroside significantly ($p<0.05$) inhibited p38 phosphorylation by 65.8±2%. Further, tiliroside (6μM) inhibited MAPKAPK2 phosphorylation by 39.9±1%. Taken together, these results suggest that tiliroside suppresses neuroinflammation by interfering with MAP kinase and NF-κB signaling pathways.

1. Tsukamoto, S., et al., *Isolation of cytochrome P450 inhibitors from strawberry fruit, Fragaria ananassa.* Journal of natural products, 2004. **67**(11): p. 1839-41.

2. Matsuda, H., et al., *Hepatoprotective principles from the flowers of Tilia argentea (linden): structure requirements of tiliroside and mechanisms of action.* Bioorganic & medicinal chemistry, 2002. **10**(3): p. 707-12.