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## Differential effects of grape seed extract on inflammatory responses of microglial cells

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Microglial activation has been linked to multiple pathologies, including Alzheimer's disease and cerebral ischemia. Nitric oxide (NO) production by inducible nitric oxide synthase (iNOS) and superoxide from NADPH oxidase (NOX) in microglial cells have been regarded as a dual-key mechanism underlying neuro-inflammatory responses leading to neuronal damage. NO reacts with superoxide to produce peroxynitrite, a highly cytotoxic anion. Antioxidants, including resveratrol extracted from grape skin, have previously been shown to attenuate both superoxide and NO production in activated microglia. A mixture of polyphenols found in grape seed extract (GSE) also possess powerful antioxidant properties. Both resveratrol and GSE have been shown to attenuate neuronal death and neuro-behavioral deficits in rodent stroke models. In this study, we tested the hypothesis that GSE is an anti-inflammatory agent capable of suppressing NO production in microglial cells induced by interferon-gamma (IFN-gamma) and lipopolysaccharide (LPS). GSE suppressed LPS-induced NO production, but surprisingly promoted IFN-gamma-induced NO production in a dose-dependent manner. At higher concentrations, GSE alone induced NO production. More importantly, in the presence of IFN-gamma, higher concentrations of GSE led to cell death. These results suggest that GSE can either alleviate or exacerbate inflammatory conditions, depending on the types of agonists and inductions.