Title: Marinobufagenin reduces oxidative stress and pro-inflammatory cytokines in the cortex and hippocampus of LPS-challenged mice.

Authors: Eduarda De Paula Ferreira Invernizzi Neves[1], Rivia Regina Lopes Da Silva[1], Evelyn Rayani Araújo Farias[1], Millena Ferreira Rodrigues Fonseca[1], Victoria Francelino Alves[2], Martina Raissa Ribeiro[2], Hericles Mesquita Campos[1], Robbert Mota Pereira[1], Paulo Cesar Ghedini[1], Renata Mazaro e Costa[1], Cristoforo Scavone[2], Luís E. M. Quintas[3], Jacqueline Alves Leite[1].

[1]Department of Pharmacology, Institute of Biological Sciences, Universidade Federal de Goiás, Goiânia, Brazil.
[2]Departament of Pharmacology, Institute of Biomedical Sciences, University of São Paulo.
[3]Laboratory of Biochemical and Molecular Pharmacology, Institute of Biomedical Sciences, Health Sciences Center, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro.

Introduction: The biochemical integrity of the brain is essential for normal central nervous system (CNS) function. Oxidative stress, caused by excessive free radicals and inadequate antioxidant response, contributes to brain degradation. This stress is linked to neuroinflammation, with macrophages/microglia and astrocytes producing reactive oxygen species that lead to neurodegenerative and neuropsychiatric diseases. Cardiac glycosides (CGs), such as marinobufagenin (MBG), bind to Na+/K+-ATPase to transport Na+ and K+. MBG, an endogenous cardiotonic agent, shows anti-inflammatory effects in zymosan-induced inflammation models. This study evaluated MBG's neuroprotective effect on LPS-induced oxidative stress in the cortex and hippocampus and its correlation with pro-inflammatory cytokines. **Methods:** The experimental procedures were approved by the Animal Ethics Committee of the Federal University of Goiás (CEUA/UFG Protocol No. 014/21). Swiss mice were pre-treated for 3 consecutive days with MBG (0.56 mg/kg i.p.), and 1 hour after the last day of treatment, the animals were challenged with LPS (1 mg/kg i.p.). Antioxidant parameters were evaluated in samples of the total cortex and hippocampus after euthanizing the animals, 24 hours after the LPS challenge. **Results:** MBG showed antioxidant action by decreasing lipid peroxidation by 31% and 60% and protein carbonylation by 32% and 49% in the total cortex and hippocampus respectively. Furthermore, in total cortex MBG restored the activity of catalase by 49 % and superoxide dismutase by 80% when compared with LPS group. Similar results were observed for the hippocampus. Meanwhile, the MBG in these structures induced a decrease in the IL-1β and TNFα levels. **Conclusion:** These results highlight the antioxidant potential of MBG and suggest that it is capable of reducing the oxidative effects and pro-inflammatory cytokines associated with acute LPS exposure. Further additional studies are necessary to elucidate a signaling pathway induced by MBG in LPS-induced neuroinflammation. **Financial support:** CNPq.