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Budlein A ameliorates monosodium urate-induced gout arthritis in mice

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Introduction and objectives: Gout is one of the most painful inflammatory disease that is induced by the deposition of monosodium urate (MSU) crystals in the joints and peri-articular tissues.[1] Budlein A (BudA) is a sesquiterpene lactone with analgesic and anti-inflammatory properties related to the inhibition of pro-inflammatory cytokines and leukocytes recruitment.[2] This work evaluated the efficacy of BudA isolated from *Viguiera robusta* (Asteraceae) in a model of MSU-induced gout arthritis in mice. Material and methods: Male Swiss mice were used in accordance to the State University Ethics Committee on Animal Research and Welfare approval (process number 14544.2013.44). Mice were treated with BudA (1 or 10 mg/kg, per oral) or vehicle 1h before stimulus with MSU (100 µg/10 µl, intra-articular). Mechanical hyperalgesia (electronic pressure-meter test) and knee joint edema (caliper) were evaluated 1-15 h after MSU. These data were analyzed using two-way ANOVA followed by Tukey post-test. Leukocyte recruitment was evaluated 15 h after stimulus by counting total leukocytes (Neubauer chamber) and in the histopathological analysis (HE staining).[3] Pro-inflammatory cytokines IL-1β and TNF-α and the components of the inflammasome platform NLRP3, ASC, and caspase-1 were evaluated by RT-qPCR. Elisa was used to evaluate NF-κB activation. *In vitro* analysis was performed using bone marrow-derived macrophages (BMDMs) LPS-primed (stimulated with MSU crystals) for determination of mature IL-1β in the supernatant by ELISA. For these experiments, BMDMs were incubated with BudA at concentrations 1-10 µg/ml. These data were analyzed using one-way ANOVA followed by the Tukey post-test. Results: BudA at 10 mg/kg reduced mechanical hyperalgesia and edema; decreased total leukocytes recruitment in 57% and reduced inflammatory infiltrate as observed in the HE staining in 60%. Furthermore, BudA reduced the mRNA expression of IL-1β and TNF-α both *in vivo* (50% and 60%, respectively) and *in vitro* (41% and 65%, respectively). Further, BudA inhibited the expression of the inflammasome components NLRP3 in 50%, ASC in 44%, and caspase-1 in 52% and reduced NF-κB activation in 40%. Conclusion: Treatment with BudA improves MSU-induced gout arthritis by reducing leukocytes recruitment, NF-κB activation and downstream targets. *In vitro*, BudA reduced IL-1β maturation in MSU stimulated BMDMs. Thus, BudA certainly deserves further studies on its pre-clinical and clinical applicability.

Keywords: experimental arthritis, synovitis, NLPR3 inflammasome
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