

Dissection of anti-inflammatory and immunomodulatory activity of *Mangifera indica* L. reveals the modulation of mPGES-1/PPAR γ axis and Th17/Treg ratio.

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Abstract

Background and Purpose: In the context of inflammation and immunity, there are fragmented and observational studies relating to the pharmacological activity of *Mangifera indica* L. and its main active component mangiferin. We, therefore, aimed to evaluate the potential beneficial effects of this plant extract (MIE, 90% in mangiferin) in a mouse model of gouty arthritis, dissecting the cellular immune phenotypes and the biochemical mechanism/s beyond its activity. **Experimental Approach:** Gouty arthritis was induced by the intra-articular administration of MSU crystals (200 μ g 20 μ l-1). MIE (0.1-10 mg kg $^{-1}$) or corresponding vehicle (DMSO/saline 1:3) were orally administrated concomitantly to MSU (time 0), 6 and 12 h after the stimulus. Thereafter, knee joint score and oedema were evaluated in addition to western blot analysis for several components of mPGES-1/PPAR γ pathway. Moreover, the analysis of pro/anti-inflammatory cyto-chemokines coupled to the assessment of the cellular infiltrate's phenotype was investigated. **Key Results:** Treatment with MIE revealed a dose-dependent reduction in joint inflammatory scores with maximal inhibition observed at 10 mg kg $^{-1}$. MIE significantly reduced leukocyte infiltration and activation and the expression of different pro-inflammatory cyto-chemokines in inflamed tissues. Furthermore, biochemical analysis revealed that MIE modulated COX-2/mPGES-1 and mPGDS-1/PPAR γ pathways. Flow cytometry analysis also highlighted a prominent modulation of infiltrating inflammatory monocytes (CD11b+ve/CD115+ve/LY6Chi), and (both infiltrated and circulating) Treg cells (CD4+ve/CD25+ve/FOXP3+ve) after MIE treatment. **Conclusion and Implications:** Collectively, the results of this study demonstrate a novel function of MIE to positively affect the local and systemic inflammatory/immunological perturbation in the onset and progression of gouty arthritis.

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