Quercetin Reduces Inflammatory Pain: Inhibition of Oxidative Stress and Cytokine Production

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Figure S1. The antihypernociceptive effect of quercetin (**1**) depends on pré-treatment time. Mice were treated with **1** (100 mg/kg, 30 min, intraperitoneal) or vehicle (Tween 80 20% in saline) at different time points (12, 6 or 3 h, or 30 min) before the subcutaneous plantar injection of carrageenin (100 µg/paw). The intensity of hypernociception was measured 1, 3 and 5 h after carrageenin injection by the electronic pressure-meter test ($n = 5$). [$* p < 0.05$ compared with the saline group, $** p < 0.05$ compared to the vehicle group (one-way ANOVA followed by Tukey test)].

Figure S2. Quercetin (**1**) inhibits carrageenin-induced paw edema. Mice were treated with **1** (100 mg/kg, 30 min, intraperitoneal) or vehicle (Tween 80 20% in saline) before the subcutaneous plantar injection of carrageenin (100 µg/paw). The paw edema was evaluated 30 min, 1, 2 and 3 h after stimulus injection using a calliper ($n = 5$). [$* p < 0.05$ compared with the saline group, $** p < 0.05$ compared to the vehicle group (one-way ANOVA followed by Tukey test)].

Figure S3. Treatment with quercetin (**1**) treatment did not affect carrageenin-induced neutrophil recruitment or TNF α and CXCL1 production. Mice were treated with **1** (100 mg/kg, 30 min, intraperitoneal, 30 min) or vehicle (Tween 80 20% in saline) before the subcutaneous plantar injection of carrageenin (100 μ g/paw). Three hours after carrageenin injection, mice were sacrificed and paw skin samples were collected for the determination of myeloperoxidase activity (Panel A), and TNF α (Panel B) and CXCL1 (Panel C) production ($n = 5$). [$* p < 0.05$ compared with the saline group (one-way ANOVA followed by Tukey test)].

Figure S4. Treatment with quercetin (**1**) did not reduce TNF α - and CXCL1-induced neutrophil recruitment or the hypernociception induced by direct-acting hypernociceptive mediators (PGE $_2$ and dopamine). Mice were treated with **1** (100 mg/kg, 30 min, intraperitoneal) or vehicle (Tween 80 20% in saline) before cytokine (TNF α 300 pg/paw or CXCL1 20 ng/paw, Panel A), PGE $_2$ (100 ng/paw, Panel B) or dopamine (10 μ g/paw, Panel B) injection. The myeloperoxidase activity was determined in samples of paw skin collected 3 h after cytokine injection (Panel A). The intensity of mechanical hypernociception was measured 3 h after stimulus injection by the electronic pressure-meter test (Panel B). ($n = 5$). [$* p < 0.05$ compared with the saline group (one-way ANOVA followed by Tukey test)].