

Modulatory activity of flavonoids in production of reactive oxygen species from neutrophils of patients with rheumatoid arthritis

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Introduction: Rheumatoid arthritis (RA) is a chronic disease characterized by synovial tissue inflammation, where neutrophils (PMN) are the most abundant cells and are important mediators of tissue destruction. Tissue damage in AR involves excessive production of reactive oxygen species (ROS) triggered by immune complexes (IC) and neutrophils interactions via receptors Fc γ R and complement receptors (CR). Modulation of both the effector potential of these receptors and ROS generation may be relevant to the maintenance of body homeostasis. Compounds as flavonoids have been considered helpful to inhibit and/or modulate the oxidative damage associated with PMN. **Objective:** In this study, we evaluated the neutrophil oxidative burst, specifically stimulated via Fc γ R and Fc γ R/CR receptors, from RA patients at active disease stages treated with anti-TNF (infliximab) and the ability of flavonoids (quercetin and galangin) to inhibit the ROS production on these cells. **Methods:** Human peripheral blood was collected from the healthy volunteers and RA patients treated with anti-TNF using Alsever solution. Neutrophils were isolated in a gelatin gradient. The cells were stimulated with IC rabbit anti-OVA IgG (IC-IgG) for the via Fc γ R and IC opsonized with healthy human autologous serum (CHS-IC) or IC opsonized with RA human own serum (RAHS-IC) for the via Fc γ R/CR receptors. The ROS generation were evaluated through the luminol chemoluminescence assays (CL-lum). This assay was used to evaluated the flavonoids effects. **Results:** Results showed that the oxidative burst mediated by Fc γ R (IC-IgG) and Fc γ R/CR (CHS-IC or RAHS-IC) resulted in increased ROS production in patients with active RA when compared than the healthy controls what reflect of Fc γ R/CR higher cooperation in cells of patients. The neutrophils treated with flavonoids, quercetin (q) and galangin (g) inhibit the production of ROS manner concentration dependent. When neutrophils were stimulated with IC-IgG the quercetin showed inhibitory effect for the production of ROS in patients and controls (IC₅₀q: patient 3,06 μ M; controls 1,70 μ M; IC₅₀g: patients 4,40 μ M; controls 2,4 μ M). However, when neutrophils were stimulated with the CHS-IC or RAHS-IC via Fc γ R/CR, the galangin had its effect equaled to that of quercetin (IC₅₀q: patient 2,84 μ M; control 2,01 μ M; IC₅₀g: patient 3,56 μ M; control 2,12 μ M). **Conclusion:** Flavonoids showed a modulation in ROS production, especially galangin that showed a inhibitory effect when neutrophils are stimulated with ICopsonized with human autologous serum of patients with RA. Thus, this study can contribute for the understanding of the mechanisms involved in the pathogenesis of the RA, which might become potential targets for the development of specific therapeutic agents for this disease.

Keywords: Neutrophils, rheumatoid arthritis, oxidative stress, Fc-gamma and CR receptors, flavonoids.

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