Bergamot-derived phase II metabolites modulate inflammation and muscle differentiation markers in C2C12 cells under inflammatory and sarcopenia-like conditions

Simone Perna[1], Jessica Capraro[1], Alessio Scarafoni[1], Patrizia Riso[1], Giovanna Baron2

1Division of Human Nutrition, Department of Food, Environmental and Nutritional Sciences (DeFENS), Università degli Studi di Milano, Milano, Italy, Milano, Italy,
2Department of Pharmaceutical Sciences - DISFARM University of Milan, Milano, Italy

Abstract

Background and Objectives
Bergamot (Citrus bergamia) is rich in bioactive polyphenols, such as naringin and hesperidin, which are metabolized into naringenin and hesperetin phase II derivatives. These metabolites are the primary circulating forms and have shown anti-inflammatory and myoprotective potential. This study aimed to evaluate the effects of bergamot-derived phase II metabolites on inflammatory markers and skeletal muscle differentiation in murine C2C12 myoblasts under LPS-induced inflammation and DEXA-induced sarcopenia-like conditions.

Methods
C2C12 myoblasts were treated with varying concentrations of naringenin and hesperetin (0, 0.1, and 1 mg/dL). Key inflammatory markers (e.g., TNF-alpha, IL-8) and muscle differentiation markers (e.g., MYOD1, Myogenin, N-cadherin) were assessed. Stress-responsive pathways (ERK1/ERK2, AMPK alpha-1/2) and energy metabolism regulators were also evaluated.

Results
Bergamot-derived metabolites demonstrated dose-dependent modulation of inflammatory pathways, significantly reducing TNF-alpha activity, a known inhibitor of myogenesis via NF-κB. Muscle differentiation markers (MYOD1, Myogenin) and regeneration markers (IL-8, N-cadherin) were upregulated, indicating enhanced myogenic capacity. Stress-responsive pathways (ERK1/ERK2, AMPK alpha-1/2) were also influenced, suggesting improved muscle resilience under inflammatory and sarcopenia-like conditions.

Discussion
The findings highlight the dual role of bergamot-derived phase II metabolites in mitigating cytokine-driven inflammation while promoting skeletal muscle differentiation and regeneration. These results align with prior evidence of bergamot polyphenols' anti-inflammatory properties and extend their therapeutic relevance to muscle health. The potential application of bergamot metabolites in musculoskeletal therapies for conditions such as sarcopenia and chronic inflammation warrants further preclinical studies to elucidate underlying mechanisms and validate efficacy.
Keywords: bergamot, inflammation, muscle differentiation, phase II metabolites, C2C12 cells