Colonic (poly)phenol metabolites as promising tools to control inflammation and prevent cardiovascular disease

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https://doi.org/10.56095/eaj.v5i1.129
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Aim: Chronic inflammation underlies numerous diseases, including atherosclerosis. The identification of anti-inflammatory agents, particularly from dietary sources, is of great interest for the development of functional products targeting early stages of chronic inflammatory conditions. This study investigated the *in vitro* anti-inflammatory activity of chiral phenyl-γ-valerolactones, the main colonic metabolites of flavan-3-ols.

Methods: Human dermal fibroblasts were treated with 10 phenyl-γ-valerolactones (1 µM) for 48 hours. Compounds included pure enantiomers and methylated or sulfated derivatives, tested at concentrations representative of plasma levels following dietary intake. During the first 24 hours, cells were treated under basal conditions; during the second 24 hours, treatments were repeated in the presence or absence of lipopolysaccharide (LPS, 1 µg/mL). Cytotoxicity was assessed by MTT and lactate dehydrogenase assays (LDH). Anti-inflammatory activity was evaluated by measuring IL-6 and IL-8 secretion using ELISA, with data normalized to protein content (bicinchoninic acid assay). To investigate the underlying mechanism of action, NF-κB activation was assessed by western blot analysis of p65 expression, normalized to β-actin. A 24-hour pharmacokinetic study was conducted to evaluate compound biotransformation and to characterize metabolic products, monitoring 31 phenyl-γ-valerolactones.

Results: None of the tested compounds induced cytotoxicity. (4*R*)-5-(4′-hydroxyphenyl)-γ-valerolactone (R-CC01) reduced IL-6 and IL-8 secretion by 76% (p<0.001) and 70% (p<0.01), respectively, while its enantiomer (S-CC01) inhibited IL-6 by 89% (p<0.001) and IL-8 by 86% (p<0.01). (4*R*)-5-(3′,4′-dihydroxyphenyl)-γ-valerolactone (R-CC02) reduced both IL-6 and IL-8 by 83% (p<0.001). (4*S*)- and (4*R*)-5-(3′-hydroxy-4′-methoxyphenyl)-γ-valerolactones (CC03) reduced IL-6 by 90% and 78% (p<0.001), and IL-8 by 87% and 71% (p<0.01), respectively. Western blot analysis showed reduced NF-κB activation, with p65 levels decreased by 37% (R-CC01, p<0.05), 61% (R-CC02, p<0.01), and 73% (R-CC03, p<0.001). The analysis of cellular metabolism revealed that within 24 hours R-CC01 remained unmodified, whereas R-CC02 and R-CC03 formed sulfate metabolites in a time-dependent manner.

Conclusions: Phenyl-γ-valerolactones significantly reduced pro-inflammatory cytokine secretion in LPS-stimulated human fibroblasts, partly through NF-κB inhibition. These findings support their potential role in dietary or nutraceutical strategies targeting chronic inflammation.

Adipo-neuroinflammation, cognitive impairment and surrogate markers of cardiovascular risk in patients with MASLD

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Aim: The epidemiological burden MASLD have been slowly increasing in recent years. Starting from a background of metabolic dysfunction, we evaluated the associations between adipo-neuroinflammation markers (LCN2), indicators of cognitive impairment (MMSE score), surrogate cardiovascular risk indicators (RHI, IMT and MMEE), and MASLD.

Methods: In this cross-sectional study, we enrolled a group of 40 patients with a recent diagnosis of MASLD and a control group of 40 patients with no history of liver disease.

Results: Compared with the controls, patients with MASLD had higher serum levels of LCN2, lower RHI and MMEE values, and lower MMSE scores; univariate analysis also revealed that the differences between the groups in terms of heart rate, body weight, body mass index, body surface area, glycated haemoglobin, and echocardiographic variables (interventricular septal thickness, LVPWT, EF, LAVI, and E/A ratio) were statistically significant. Multinomial regression revealed that the presence of MASLD was significantly positively associated with LVPWT and LCN2, and significantly negatively associated with the RHI. With regards to assessments of cognitive impairment, the presence of MASLD was significantly negatively associated with the MMSE score. We also performed ROC curve analysis to explore the ability of RHI to predict MASLD; the results yielded an AUC of 0.826 (95% CI: 0.72–0.90; p<0.0005) at an optimal cut-off value of 1.87 (sensitivity=72.5%, specificity=90%), suggesting that the RHI can serve as a marker of endothelial dysfunction and thus as an indirect indicator of cardiovascular risk in patients with MASLD.

Conclusions: Patients with MASLD have greater cognitive impairment than controls; they also have higher serum levels of LCN-2 and greater endothelial dysfunction. These results imply that subjects with MASLD have a worse cardiovascular risk profile in addition to more pronounced cognitive impairment than controls do, thus suggesting that liver plays a greater role than simply serving as the metabolic centre.