Microbiota-derived resveratrol metabolites: new biomarkers of red wine consumption are inversely associated with inflammation in a longitudinal study of a Mediterranean population

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Background and objectives
Several studies suggest that moderate wine consumption in the context of a Mediterranean diet (MedDiet) can reduce inflammatory biomarkers related to atherosclerosis. The aim of the present study is to evaluate the association between urinary microbiota-derived resveratrol metabolites, which may serve as specific biomarkers of red wine consumption, and plasma circulating proinflammatory molecules.

Methods
This study included 179 participants at high cardiovascular risk (mean age 69 years, 49% women) enrolled in the PREDIMED trial who were moderate red wine consumers (mean intake 62.1 mL/d). Plasma inflammatory biomarkers and urinary dihydroresveratrol sulfate (DHRs) and glucuronide (DHRg) were analyzed using xMAP technology and high-performance liquid chromatography coupled to mass spectrometry, respectively. Receiver operating characteristic (ROC) analyses were performed to evaluate dihydroresveratrol metabolites as biomarkers of red wine consumption. Multivariable regression analyses were used to assess the relationship between baseline values and 1-year changes in urinary dihydroresveratrol metabolites and plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α) and monocyte chemoattractant protein-1 (MCP-1).

Results
Baseline characteristics of the participants are presented by sex in *Table 1*. ROC curves confirmed that urinary DHRg and DHRs are reliable biomarkers of red wine consumption [AUC = 0.835, and AUC = 0.803, respectively]. As shown in *Figure 1*, baseline urinary DHRs were negatively associated with sVCAM-1 ($p = 0.012$). After one year of follow-up, changes in urinary DHRg also showed a negative association with sVCAM-1 ($p = 0.028$).

Discussion
Our findings demonstrate that urinary DHRg and DHRs are reliable and specific biomarkers of red wine consumption, which were inversely associated with circulating sVCAM-1, a recognized biomarker of atherosclerosis progression.

Table 1

Baseline characteristics of the participants by sex (n = 179).

	All (n=179)	Men (n=91)	Women (n=88)	*p*-value
Age, years	68.9 ± 5.9	58.3 ± 6.4	69.5 ± 5.4	0.177
BMI, kg/m^2	**29.5 ± 3.6**	**28.9 ± 3.3**	**30.2 ± 3.8**	**0.016**
Overweight (BMI≥25kg/m^2), n (%)	162 (90.5)	81 (89.0)	81 (92.0)	0.492
Physical activity, METs-min/d	**267.2 ± 214.0**	**354.0 ± 232.0**	**177.5± 148.1**	**<0.001**
Current smoker, n (%)	**26 (14.5)**	**24 (26.4)**	**2 (3.2)**	**<0.001**
Medication, n (%)				
NSAIDS	12 (6.7)	4 (4.4)	8 (9.1)	0.209
Aspirin intake	42 (23.5)	20 (22.0)	22 (25.0)	0.636
Other antiplatelet drugs	37 (20.7)	20 (22.0)	17 (19.3)	0.660
Diuretics	38 (21.2)	14 (15.4)	24 (27.3)	0.052
Insulin	14 (7.8)	5 (5.5)	9 (10.2)	0.238
Antidepressants	**42 (23.5)**	**11 (12.1)**	**31 (35.2)**	**<0.001**
ACE inhibitors	50 (27.9)	26 (28.6)	24 (27.3)	0.846
Oral hypoglycemic drugs	**58 (32.4)**	**36 (39.6)**	**22 (25.0)**	**0.037**
Vitamins or supplements	**20 (11.2)**	**5 (5.5)**	**15 (17.0)**	**0.003**
Educational level, n (%)				0.051
Low	135 (75.4)	63 (69.2)	72 (81.8)	
High & medium	44 (24.6)	28 (30.8)	16 (18.2)	
Diabetes mellitus, n (%)	89 (49.7)	51 (56.0)	38 (43.2)	0.085
Dyslipidemia, n (%)	116 (64.8)	56 (62.5)	60 (68.2)	0.352
Hypertension, n (%)	146 (81.6)	73 (80.2)	73 (83.0)	0.637
Family history premature CHD, n (%)	**43 (24.0)**	**15 (16.5)**	**28 (31.8)**	**0.016**
Total energy intake, kcal/d	**2353.8 ± 634.1**	**2548.8 ± 634.8**	**2152.1 ± 570.0**	**0.001**
Intervention group, n (%)				0.110
MedDiet supplemented with EVOO	60 (33.5)	33 (36.2)	27 (30.7)	
MedDiet supplemented with nuts	63 (35.2)	36 (39.6)	27 (30.7)	
Low-fat diet control group	56 (31.3)	22 (24.2)	34 (38.6)	
Wine consumption (mL/d)	**85.8 ± 135.4**	**134.8 ± 159.6**	**35.1 ± 77.7**	**<0.001**
Red wine consumption (mL/d)	**62.1 ± 110.0**	**101.3 ±134.3**	**21.6 ± 53.2**	**<0.001**
Grape & raisin consumption (g/d)	11.2 ± 20.0	10.7 ± 16.7	11.8 ± 23.1	0.706
Dihydroresveratrol glucuronide (nmol/mL)	1.1 ± 2.9	1.5 ± 3.7	0.7 ± 1.4	0.054
Dihydroresveratrol sulfate (nmol/mL)	1.6 ± 5.8	2.4 ± 8.0	0.9 ± 1.7	0.080
sVCAM-1 (ng/mL)	188.1 ± 51.9	194.1 ± 57.7	182.1 ± 45.3	0.258
sICAM-1 (ng/mL)	180.0 ± 72.6	167.7 ± 66.3	192.3 ± 77.0	0.070
IL-6 (pg/mL)	5.0 ± 3.2	5.0 ± 3.4	5.0 ± 3.0	0.957
TNF-α (pg/mL)	12.7 ± 20.2	11.1 ± 11.0	14.4 ± 26.9	0.365
MCP-1 (pg/mL)	39.3 ± 22.5	39.3 ± 19.0	39.3 ± 26.0	0.993

Data are given as mean ± standard deviation (SD) for continuous variables, and *n* (percentage) for categorical variables.
BMI, body mass index.; d, day; EVOO, extra virgin olive oil; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; MedDiet, Mediterranean diet; METs, metabolic equivalent of tasks; NSAIDS, non-steroidal anti-inflammatory drugs; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; TNF-α, tumor necrosis factor-α. $p < 0.05$ were considered significant. Student's t-test were used for continuous variables and a chi-square test was used for categorical variables.

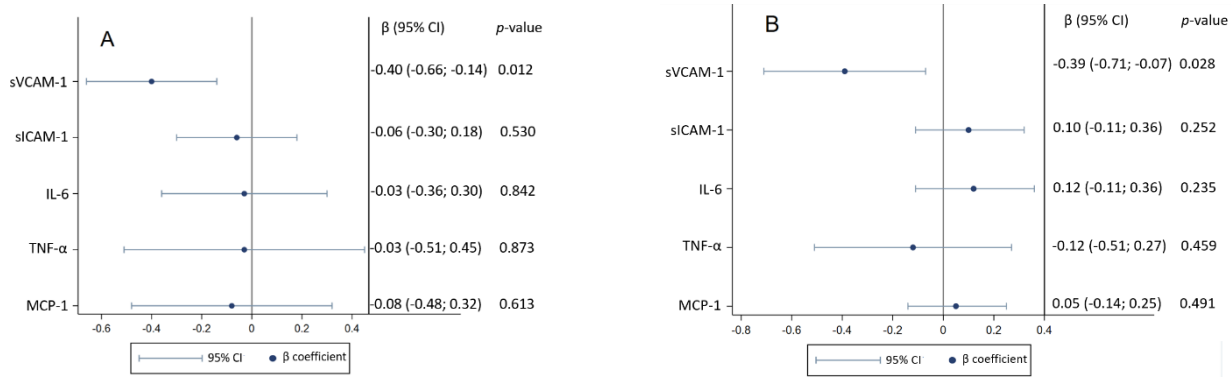

Figure 1. Multivariable-adjusted regression between baseline dihydroresveratrol sulfate in urine and inflammatory molecules (ng/mL per 1-SD increment) (**A**) and multivariable-adjusted regression between one-year changes in dihydroresveratrol glucuronide in urine and inflammatory molecules (ng/mL per 1-SD increment) (**B**). Regressions were adjusted for age, sex, recruitment center, intervention group (only **B**), physical activity, smoking habit, BMI, diabetes, hypercholesterolemia, hypertension, and intake of energy, omega-3 fatty acids, statins, aspirin, grapes and raisins. Analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation. sVCAM-1, soluble vascular cell adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; IL6, interleukin-6; TNF-α, tumor necrosis factor- a; MCP-1, monocyte chemoattractant protein-1.

Summarized Curriculum Vitae

Francesc M. Campins-Machado (ORCID: 0009-0006-2162-1756) graduated in Food Science and Technology from the University of Barcelona (UB) in 2021, receiving the Extraordinary Degree Award. Subsequently, he pursued a Master's degree in Nutrition Applied to Physical Activity at the Open University of Catalonia (UOC) during the 2023-2024 academic year. He is currently undertaking a PhD in Food and Nutrition at UB, where he is researching the phenolic content of various foods from the Mediterranean diet (MedDiet), including wine and extra virgin olive oil (EVOO). His forthcoming research will focus on the effect of temperature on EVOO and refined olive oil.