The Journal of Nutrition, Health and Aging 28 (2024) 100003

Contents lists available at ScienceDirect

The Journal of Nutrition, Health and Aging

journal homepage: www.elsevier.com/locate/jnha

Original Article

Moderate wine consumption measured using the biomarker urinary tartaric acid concentration decreases inflammatory mediators related to atherosclerosis

Inés Domínguez López [a,b,c], Camila Arancibia-Riveros [a,b], Rosa Casas [b,c,d], Polina Galkina [a,b], Maria Pérez [a,b,c], Miguel Ángel Martínez-González [c,e], Montserrat Fitó [c,f], Emilio Ros [c,g], Ramon Estruch [b,c,d,**], Rosa M. Lamuela-Raventós [a,b,c,*]

[a] Polyphenol Research Group, Departament de Nutrició, Ciències de l'Alimentació i Gastronomía, Facultat de Farmacia, Universitat de Barcelona (UB), Av. de Joan XXII, 27-31, 08028 Barcelona, Spain
[b] Institut de Nutrició i Seguretat Alimentària (INSA), Universitat de Barcelona (UB), 08921 Santa Coloma de Gramanet, Spain
[c] CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, 28029 Madrid, Spain
[d] Department of Internal Medicine, Hospital Clinic, Institut d'Investigació Biomèdica August Pi i Sunyer (IDIBAPS), University of Barcelona, 08036 Barcelona, Spain
[e] Department of Preventive Medicine and Public Health, University of Navarra, IdiSNA, 31008 Pamplona, Spain
[f] Unit of Cardiovascular Risk and Nutrition, Institut Hospital del Mar de Investigaciones Médicas (IMIM), 08007 Barcelona, Spain
[g] Lipid Clinic, Endocrinology and Nutrition Service, Institut d'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clínic, 08036 Barcelona, Spain

ARTICLE INFO

Keywords:
Biomarker
Inflammation
Mediterranean diet
Alcohol
Bioactive

ABSTRACT

Objectives: Several studies suggest that moderate wine consumption, particularly red wine, may have benefits for cardiovascular health. Red wine contains a variety of bioactive compounds, including polyphenols like phenolic acids, which have demonstrated anti-inflammatory effects in experimental models. The aim of this study was to assess the anti-inflammatory properties of wine, measured as urinary tartaric acid, a new biomarker of wine consumption.
Design, settings, and participants: One-year longitudinal study that included 217 participants from the PREDIMED trial.
Measurements: Plasma inflammatory biomarkers and urinary tartaric acid were analyzed using xMAP technology and high-performance liquid chromatography, respectively. Multivariable regression analyses were performed to assess the relationship between variations over 1-year in urinary tartaric acid concentrations and 1-year changes in serum inflammatory molecules, including adhesion cell molecules, interleukine-6, tumour necrosis factor alpha, and monocyte chemotactic protein 1. Three categories were built according to tertiles of 1-y changes in urinary tartaric acid.
Results: Using a ROC curve, urinary tartaric acid was corroborated as a reliable biomarker of wine consumption (AUC = 0.818 (95% CI: 0.76; 0.87). In the continuous analysis, participants with higher increases in tartaric acid significantly reduced their concentrations in soluble vascular adhesion molecule (sVCAM-1) after 1-year of follow-up (−0.20 (−0.38; −9,93) ng/mL per 1-SD increment, *p*-value = 0.031). Moreover, tertiles 2 and 3 of 1-year changes in tartaric acid presented a significant reduction in soluble intercellular cell adhesion molecule (sICAM-1) as compared to tertile 1 (−0.31 (−0.52; −0.10) ng/mL, *p*-value = 0.014 and −0.29 (−0.52; −0.07) ng/mL, *p*-value = 0.023, respectively). Participants in the third tertile also exhibited a reduced concentration of sVCAM-1 compared to those in the first tertile (−0.31 (−0.55; −0.06) ng/mL, *p*-value = 0.035).
Conclusions: Our findings suggest that wine consumption is associated with lower levels of inflammation due to the anti-inflammatory properties of wine compounds.
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Abbreviations: CVD, cardiovascular disease; CRP, C-reactive protein; sICAM-1, soluble intercellular adhesion molecule-1; IL-6, interleukin-6; MedDiet, Mediterranean diet; MCP-1, monocyte chemoattractant protein-1; NSAID, non-steroidal anti-inflammatory drug; ROC, receiver operating characteristic; T, tertile; TNF-α, tumour necrosis factor alpha; VCAM-1, soluble vascular cell adhesion molecule-1.

* Corresponding author at: Department of Nutrition, Faculty of Pharmacy, University of Barcelona, Av. Joan XXIII, 27-31, 08028 Barcelona, Spain.
** Corresponding author at: Department of Internal Medicine, Hospital Clinic, Barcelona, Spain.
E-mail addresses: restruch@clinic.cat (R. Estruch), lamuela@ub.edu (R.M. Lamuela-Raventós).

http://doi.org/10.1016/j.jnha.2023.100003
Received 23 October 2023; Received in revised form 20 November 2023; Accepted 21 November 2023
Available online 6 December 2023
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1. Introduction

Inflammation and its multifaceted role in health establish a fundamental link between the body's immune response and various physiological processes [1]. While acute inflammation is a protective mechanism aimed at repairing tissue damage and combating infections, chronic inflammation can lead to a cascade of detrimental effects, including the development of arthritis, asthma, atherosclerosis, autoimmune diseases, cancer, diabetes, and obesity [2–4].

Within this framework, the Mediterranean diet (MedDiet) has garnered attention for its potential to curb inflammation. Epidemiological studies have demonstrated the effectiveness of the MedDiet in reducing circulating inflammatory molecules in a population at high cardiovascular (CVD) risk [5,6]. This plant-based dietary pattern is rich in antioxidant-rich fruits, vegetables, whole grains, healthy fats from sources like extra virgin olive oil and fatty fish and includes a moderate consumption of wine [7]. Some of its dietary components, such as polyphenols and omega-3 fatty acids, exhibit powerful anti-inflammatory properties, potentially helping to modulate inflammatory processes responsible of several chronic diseases [8–10]. In the context of the MedDiet, the moderate intake of alcohol (ethanol), mainly as wine, emerges as a complementary factor that synergizes with other heart-protective elements of the MedDiet. These components may contribute to the elevation of high-density lipoprotein (HDL)-cholesterol, the inhibition of platelet aggregation, the stimulation of antioxidant effects, and the reduction of systemic inflammation, among other effects [11].

A contentious debate persists concerning the impact of red wine consumption on health. Both epidemiological and clinical findings seem to emphasize the beneficial role of moderate red wine consumption in reducing inflammation [12]. Nonetheless, some studies did not find any noticeable impact of moderate red wine consumption on inflammatory biomarkers [13], while others even have reported proinflammatory effects [14]. However, most randomized clinical trials and observational epidemiological investigations strongly suggest that moderate drinking of wine yields positive outcomes in various inflammatory pathways linked to endothelial activation [15–18]. This connection could potentially be attributed to the presence of polyphenols, which have the capacity to alleviate mild inflammation and endothelial activation.

Consumption of wine, the main alcoholic beverage in the MedDiet, in epidemiological and clinical trials is primarily assessed using food frequency questionnaires, which might be affected by subjectivity [19]. In contrast, urinary tartaric acid concentration has emerged as an objective, reliable, selective, and sensitive biomarker for gauging moderate wine consumption [20]. The aim of the present study, nested in the PREDIMED trial, was to analyse the relationship of changes in wine consumption, measured with the reliable biomarker tartaric acid excreted in urine, with changes in plasma circulating inflammatory molecules in an older population at high CVD risk of the PREDIMED trial, using repeated measurements at baseline and after one year of follow-up.

2. Methods

2.1. Study design

A prospective cohort analysis was conducted utilizing baseline and one-year data from the PREDIMED (PREvención con Dieta MEDiterránea) study. This large, parallel-group, multicenter, randomized, controlled, five-year clinical trial aimed to assess the impact of the MedDiet enriched with olive oil or nuts on the incidence of CVD. The trial took place in Spain from October 2003 to December 2010 and involved 7447 participants at high cardiovascular risk (www.predimed.es).

Eligible participants included men (aged 55–80 years) and women (aged 60–80 years) with type-2 diabetes or exhibiting at least three of the following significant risk factors: current smoking, hypertension, dyslipidemia, overweight/obesity, or a family history of premature CVD. Detailed methodologies and participant criteria have been previously published [21,22].

The present substudy of the PREDIMED trial consisted of a subsample of 217 participants from the PREDIMED-Hospital Clinic of Barcelona and Navarra recruitment centres whose data regarding inflammatory biomarkers and urinary tartaric acid were available.

2.2. Ethics statement

The Institutional Review Board (IRB) of the Hospital Clinic (Barcelona, Spain) accredited by the US Department of Health and Human Services (DHHS) update for Federal-wide Assurance for the Protection of Human Subjects for International (Non-US) Institutions #00000738 approved the study protocol on July 16, 2002. All participants provided informed consent and signed a written consent form.

2.3. Covariate assessment

Food consumption was ascertained using a validated, semi-quantitative food frequency questionnaire comprising 137 items, administered by skilled dietitians [23]. To determine nutrient intakes, Spanish food composition tables were utilized.

Anthropometric measurements, including weight and height, were taken by trained staff using established techniques, enabling the calculation of body mass index (BMI) in kg/m^2. To assess physical activity levels, a validated Spanish iteration of the Minnesota physical activity questionnaire was employed, measuring metabolic equivalent tasks per minutes per day (METs min/day) [24].

2.4. Inflammatory biomarkers

Circulating inflammatory biomarkers were analysed as described elsewhere [25]. To summarize, the concentrations of soluble adhesion molecules were measured using xMAP technology on the Luminex platform (Luminex Corporation, Austin, TX, USA), according to the manufacturer's instructions, and analysed using the Bio-Plex Manager™ Software (Bio-Rad Laboratories, Inc., Hercules, CA, USA). We determined the concentration of five potential biomarkers: plasma-soluble vascular cell adhesion molecule 1 (sVCAM-1), intercellular adhesion molecule 1 (sICAM-1), interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α) and monocyte chemotactic protein 1 (MCP-1), by using a Human Cytokine Plex assay (Bio-Rad Laboratories, Inc.).

2.5. Urinary tartaric acid

Tartaric acid concentration in first spot morning urine was measured using the methodology previously described [26]. We combined data from two substudies and corrected for batch effects using an average batch correction method [26].

2.5.1. Reagents and standards

Formic acid (approximately 98%), picric acid (98%, moistened with approximately 33% water) and sodium hydroxide (>98%) were purchased from Panreac. L-(+)-Tartaric acid and creatinine were obtained from Sigma. The labelled internal standard DL-(+)-tartaric-2,3-d2 acid was purchased from C/D/N Isotopes. Solvents were high-performance liquid chromatography grade, and all other chemicals were analytical reagent grade. Ultrapure water was obtained from a Milli-Q Gradient water purification system (Millipore).

2.5.2. Sample preparation

Tartaric acid in urine was determined following a validated stable-isotope dilution LC–ESI–MS/MS method [27]. A total of 20 μL of urine were diluted 1:50 (vol:vol) with 0.5% formic acid in water, and 10 μL of

the internal standard DL-(±)-tartaric-2,3-d2 acid (200 μg/mL) were added. The diluted sample was filtered by 0.20 μm and analyzed by LC–ESI–MS/MS, following the metod described previously by Regueiro et al. [27]. The data for urinary tartaric acid were adjusted using urine creatinine levels. The creatinine levels were determined using a modified version of the Jaffé alkaline picrate method specifically designed for Thermo microtiter 96-well plates. This approach was carried out following the methodology developed by Medina-Remón et al [28].

2.5.3. LC–ESI–MS/MS analysis

The analysis was performed using an Atlantis TE C18, 100 × 2.1 mm, 3 μm (Waters, Milford, MA, USA) reversed-phase column coupled for detection to a triple quadrupole mass spectrometer API 3000 (Applied Biosystems, Foster City, CA, USA). The mass spectrometer was operated in negative electrospray ionisation. The column was maintained at 25 °C throughout the analysis. Mobile phases A and B were, 0.5% formic acid in water and 0.5% formic acid in acetonitrile, respectively. The following linear gradient was used: held at 100%A for 3.5 min, decreased to 10%A over 2 min and held for 2 min, then returned to initial conditions for 1.5 min and re-equilibrated for 6 min. The flow rate was set at 350 μL/min and the injection volume was 10 μL. Post-column addition of acetonitrile (250 μL/min) was carried out to improve analyte ionization efficiency. The detection was accomplished in the multiple reaction monitoring (MRM) mode, and the following MS/MS transitions were used for quantification and confirmation, respectively: m/z 149/87 and m/z 149/73 for tartaric acid, and m/z 151/88 and m/z 151/74 for the deuterated isotope.

2.6. Statistical analyses

Participants were divided into 3 categories according to tertiles of 1-year changes in urinary tartaric acid concentration to assess linearity. Baseline characteristics of participants are presented as means ± standard deviation (SD) for continuous variables and percentages for categorical variables. We used one-factor ANOVA to assess differences in continuous variables, and chi-squared tests for categorical values.

Individual baseline values of inflammatory biomarkers, and tartaric acid were normalized and scaled in multiples of 1 SD with Blom inverse normal transformation due to high biological variability [29]. Changes in these variables (one-year value minus the baseline value) were calculated, and the resulting difference was also normalized and scaled.

The analysis for the receiver operating characteristic (ROC) curve was obtained through a logistic regression between wine (consumers/non-consumers) as the dependent variable and urinary tartaric acid concentration as the exposure variable, adjusted for age (continuous), sex (men/women), physical activity (continuous), smoking habit (current/past/non-smoker), educational level (low/medium & high level), waist-to-height ratio (continuous), hypertension (yes/no), hypercholesterolemia (yes/no), diabetes (yes/no), energy intake (continuous), MedDiet adherence not considering wine (continuous) and grapes and raisins consumption (continuous).

Multivariable adjusted linear regression models were used to assess associations between 1-year changes of urinary tartaric acid and concentrations (analyzed as continuous variable and using tertiles) and inflammatory biomarkers per 1-SD increment. Adjustment models of increasing complexity were applied. Model 1 was minimally adjusted for age and sex. Model 2 was further adjusted for physical activity, smoking habit, educational level, waist-to-height ratio, intervention group (MedDiet supplemented with extra virgin olive oil/MedDiet supplemented with nuts/control group) diabetes, hypercholesterolemia, hypertension, and intake of aspirin and non-steroidal anti-inflammatory drug (NSAIDs) (yes/no), energy intake, MedDiet adherence (not considering wine) and consumption of grapes and raisins. To assess the linear trend (p for trend) across tertiles of tartaric acid changes, the mean value was assigned to each tertile.

All analyses were conducted with robust estimates of the variance to correct for intracluster correlation and 2-sided significance was determined at a $p < 0.05$. Analyses were performed with Stata 16.0 (Stata-Corp LP).

3. Results

3.1. General characteristics of the participants

Baseline characteristics of the participants are presented in Table 1, categorized according to tertiles of 1-year changes of urinary tartaric acid concentrations. Then mean age was 68.8 years and 52.1% were females. All groups were well balanced in terms of sex, age, and physical activity. As expected, considering the characteristics of the participants in the PREDIMED trial, all groups had a mean BMI indicating overweight and showed a high prevalence of cardiovascular risk factors; 54.8% had

Table 1
General characteristics of the participants at baseline categorized for 1-year changes in urinary tartaric acid (n = 217).

	All (n = 217)	T1 (n = 69)	T2 (n = 69)	T3 (n = 68)	p-Value
Δ Tartaric acid (μg/mg creatinine)	1.3 ± 45.2	−23.2 ± 53.7	0.9 ± 1.1	26.5 ± 45.1	
Female, n (%)	113 (52.1)	37 (49.3)	40 (55.6)	36 (50.0)	0.767
Age, years	68.8 ± 5.8	68.5 ± 5.8	69.0 ± 6.0	68.8 ± 5.6	0.887
BMI, kg/m^2	29.7 ± 3.5	29.9 ± 3.7	29.4 ± 3.6	29.7 ± 3.3	0.762
Physical activity, METS-min/day	270.9 ± 222.8	280.8 ± 254.0	259.8 ± 207.0	272.0 ± 206.3	0.851
Current smoker, n (%)	31 (14.3)	12 (16.4)	7 (9.7)	12 (16.7)	0.400
Educational level, n (%)					0.089
Low	163 (75.1)	54 (74.0)	60 (83.3)	49 (68.1)	
High & medium	54 (24.9)	19 (26.0)	12 (16.7)	23 (31.9)	
Diabetes mellitus, %	119 (54.8)	45 (61.6)	37 (51.4)	37 (51.4)	0.358
Dyslipidaemia, n (%)	138 (63.6)	47 (64.4)	44 (61.1)	47 (65.3)	0.861
Hypertension, n (%)	171 (78.8)	55 (75.3)	58 (80.6)	58 (80.6)	0.674
Total energy intake, kcal/day	2369 ± 605	2332 ± 592	2391 ± 627	2385 ± 600	0.812
Mediterranean diet adherence, 14-points score	9 ± 2	8 ± 2	9 ± 2	9 ± 2	0.264
Intervention group, n (%)					0.316
MedDiet supplemented with EVOO	80 (36.9)	28 (38.4)	28 (38.9)	24 (33.3)	
MedDiet supplemented with nuts	75 (34.6)	30 (41.1)	20 (27.8)	25 (34.7)	
Low-fat control group	62 (28.6)	15 (20.1)	24 (33.3)	23 (31.9)	
Wine consumption, mL/day	82.5 ± 127.9	100.8 ± 142.0	42.6 ± 64.5	103.7 ± 149.4	0.005
Grapes & raisins consumption (g/d)	11.2 ± 19.1	11.2 ± 20.0	11.9 ± 20.7	10.5 ± 16.5	0.912

T, tertile; BMI, body mass index.
$p < 0.05$ were considered significant.
One-ANOVA factor were used for continuous variables, and a chi-square test was used for categorical variables.

Table 2
Change in dietary intake after 1 year categorized by tertiles of change in urinary tartaric acid.

	T1 (n = 73)	T2 (n = 72)	T3 (n = 72)	p-Value
Carbohydrates (g/d)	−22.21 ± 81.81	−11.24 ± 69.66	−17.43 ± 66.81	0.661
Proteins (g/d)	−3.94 ± 21.73	0.23 ± 17.45	−3.08 ± 19.83	0.409
Total fat (g/d)	8.31 ± 33.57	5.95 ± 26.80	5.74 ± 28.00	0.845
Saturated fatty acids (g/d)	−2.52 ± 10.17	−0.44 ± 8.68	−1.19 ± 7.31	0.356
Monounsaturated fatty acids (g/d)	6.34 ± 17.27	4.83 ± 15.92	4.87 ± 14.11	0.805
Polyunsaturated fatty acids (g/d)	3.23 ± 9.41	1.49 ± 6.49	1.80 ± 10.26	0.451
Alcohol (g/d)	−2.05 ± 10.72	0.68 ± 6.76	1.28 ± 13.72	0.142
EVOO (g/d)	12.76 ± 27.10	18.09 ± 27.93	18.15 ± 24.65	0.375
Vegetables (g/d)	54.72 ± 192.82	72.15 ± 161.64	10.32 ± 170.96	0.096
Fruits (g/d)	69.57 ± 261.16	27.39 ± 185.67	14.09 ± 208.19	0.289
Cereals (g/d)	−20.75 ± 101.81	−18.03 ± 77.81	−14.16 ± 98.23	0.913
Legumes (g/d)	2.12 ± 9.17	4.43 ± 10.19	−0.18 ± 37.65	0.489
Nuts (g/d)	12.38 ± 24.52	6.69 ± 18.35	7.67 ± 26.26	0.292
Fish and seafood (g/d)	7.92 ± 38.58	7.98 ± 42.79	7.80 ± 42.08	1.000
Meat and meat products (g/d)	−15.06 ± 57.33	−12.71 ± 42.33	−22.61 ± 47.03	0.455
Dairy products (g/d)	−47.90 ± 206.55	−1.24 ± 201.55	5.77 ± 166.31	0.191
Pastries (g/d)	−7.15 ± 26.29	−9.13 ± 28.72	−1.89 ± 23.91	0.237

Data are given as mean ± standard deviation (SD); statistical analyses were undertaken using 1-factor ANOVA, $p < 0.05$ indicates statistical significance. EVOO, extra virgin olive oil; T, tertiles.

diabetes, 63.6% had dyslipidemia, and 78.8% had hypertension. Most of the participants were either non-smokers (85.7%) or had a low educational level (75.1%), equally distributed among groups. Mediterranean diet adherence was comparable among the three groups, although it tended to be lower in T1, and wine consumption was significantly lower in T2. Baseline and one-year changes in inflammatory biomarkers across tertiles of urinary tartaric acid are presented in Supplementary Tables S1 and S2, respectively.

Changes in the dietary intake of participants after one year of follow-up according to tertiles of change of urinary excretion of tartaric acid can be found in Table 2. The consumption of all foods and nutrients was well-balanced across tertiles.

3.2. Urinary tartaric acid concentration as wine consumption biomarker

After adjustments for potential confounders (age, sex, smoking habit, educational level, BMI, physical activity, intervention group, analysis time, energy intake, and grapes and raisins consumption), we found that participants who increased their consumption of wine also excreted more tartaric acid in urine (0.39 (0.28; 0.50) μg/mg creatinine per 1-SD, p-value = <0.001). Fig. 1 shows the ROC curve analysis, where it can be observed that urinary tartaric acid can predict wine consumption with an AUC = 0.818 (0.763; 0.873).

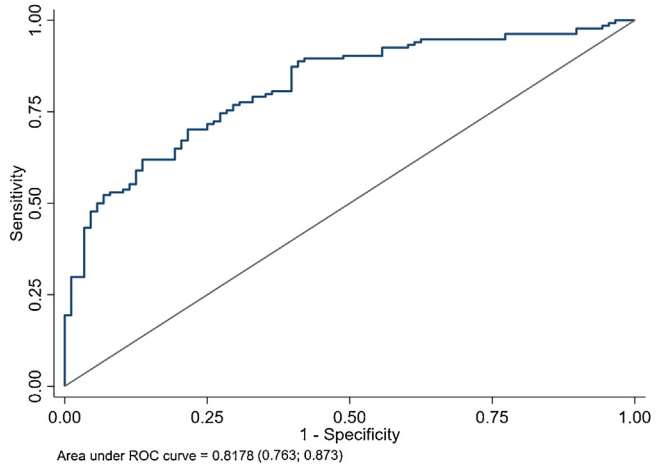

Fig. 1. Receiver operating characteristic (ROC) curves for prediction of wine consumption (yes/no) by urinary tartaric acid.

3.3. Urinary tartaric acid concentration and inflammatory molecules

As illustrated in Fig. 2, participants with higher increases in tartaric acid presented a significant reduction in sVCAM-1 concentrations after adjustment for potential confounders (−0.20 (−0.38; −0.03) ng/mL per 1-SD increase, p-value = 0.031). No other significant associations were found when changes in tartaric acid were modelled as a continuous variable.

The associations between tertiles of urinary 1-year changes in tartaric acid and 1-year changes in circulating inflammatory biomarkers are shown in Table 3. After adjustment for potential confounders in model 2, we found that an increase in urinary excretion of tartaric acid was inversely associated with changes in plasma sVCAM-1 and sICAM-1. Thus, participants in T2 and T3 had lower concentrations of sICAM-1 compared to participants of T1 (−0.31 (−0.52; −0.10) ng/mL, p-value = 0.038 and −0.29 (−0.52; −0.07) ng/mL, p-value = 0.023, respectively; p = 0.099 for trend). Similar results were found for sVCAM-1, as participants in T3 exhibited lower concentrations of the inflammatory biomarker compared to T1 (−0.31 (−0.55; −0.06) ng/mL, p-value = 0.025; p = 0.035 for trend). No other significant association was found between tertiles of change in urinary tartaric acid and changes in inflammatory biomarkers in the fully adjusted model.

4. Discussion

In this longitudinal sub-analysis within the PREDIMED trial, we assessed the anti-inflammatory potential of wine by measuring tartaric acid excretion in urine in a population at high risk for CVD. We observed an inverse association between changes in tartaric acid excretion in urine and changes in the plasma inflammatory molecules sVCAM-1 and sICAM-1.

Tartaric acid stands as the primary acid found within grapes, and during the harvest, grape juice holds between 4–8 g/L of this acid. This acid content contributes to the grapes' lower pH level and provides pleasant organoleptic characteristics to wine [30]. Intriguingly, tartaric acid is synthesized in only a limited number of plant species [31], making it a valuable compound as a biomarker for grape consumption and its derivatives, such as wine [20,32]. Our study demonstrates that urinary excretion of tartaric acid serves as a valid and reliable biomarker for assessing wine consumption, better than data obtained using validated food-frequency questionnaires. This holds substantial practical significance because assessing wine and other alcoholic beverages through food frequency questionnaires may introduce errors stemming from societal perceptions of alcohol consumption [19], and underreporting of at-risk

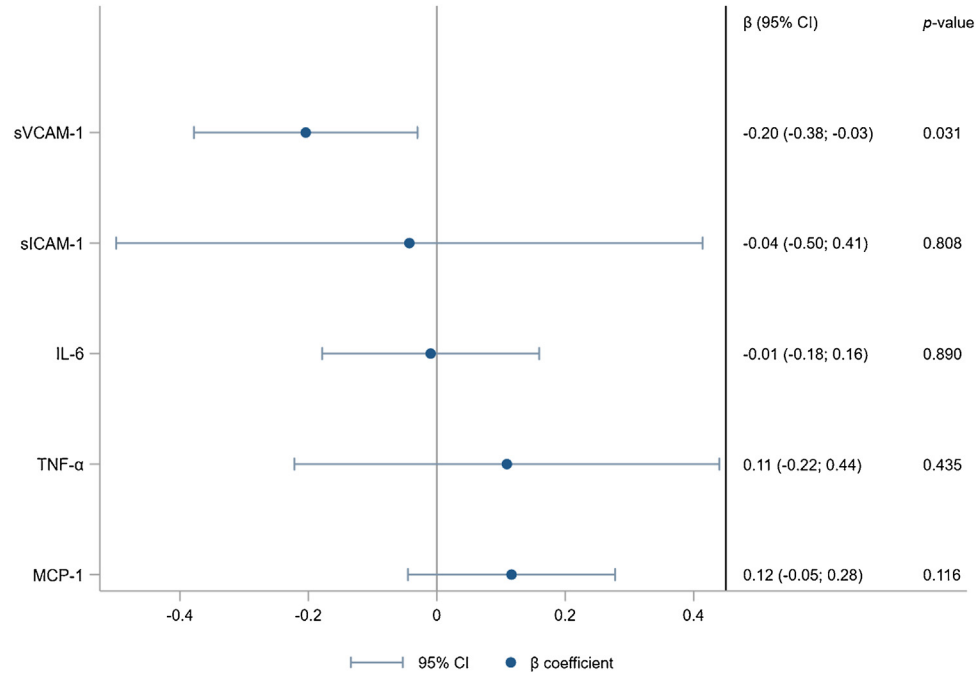

Fig. 2. Multivariable adjusted regression between 1-year changes in urinary tartaric acid and inflammatory molecules (per 1-SD increment) adjusted for age, sex, physical activity, smoking habit, waist-to-height ratio, intervention group, diabetes, hypercholesterolemia, hypertension, and intake of aspirin and NSAIDs, total energy intake, MedDiet adherence (not considering wine), grapes, and raisins. All analyses were conducted with robust estimates of the variance to correct for intracluster correlation. sVCAM-1, soluble vascular cell adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; IL6, interleukine-6; TNF-α, tumor necrosis factor- α; MCP-1, monocyte chemoattractant protein-1.

drinkers could distort the benefits of moderate drinking [33]. Apart from alcohol-related concerns, food frequency questionnaires and food records inherently entail subjectivity and the potential for inaccurate reporting, as they depend on individuals' perceptions [34]. Therefore, quantifying wine consumption through tartaric acid provides more precise and objective results.

The health effects of moderate wine consumption have been widely studied. Mendelian randomization studies suggested that the risk of CVD is decreased with a reduction of alcohol, even though the type of alcoholic beverage was not considered [35,36]. However, wine consumed during meals in the context of a MedDiet has been associated with cardioprotective effects [37], whereas these positive effects disappear with heavy episodic drinking [38]. In fact, a meta-analysis demonstrated that there is a J-shape relationship between wine consumption and vascular events and cardiovascular mortality [39]. Epidemiological studies have indicated that wine consumption is linked to a lower prevalence of metabolic syndrome and its components, including higher HDL-cholesterol, reduced lipid oxidative stress, and lower BMI [17,40,41]. In addition to its impact on the lipid profile, wine might engage other mechanisms related to inflammation that could explain its protective effects on cardiovascular health. Clinical trials provide supporting evidence for this hypothesis. Several studies have reported improvements in C-reactive protein (CRP) levels following wine consumption [42–44]. Another clinical trial involving participants with diabetes revealed a significant reduction in proinflammatory cytokines, including TNF-α, IL-6, IL-18, and CRP, after one year of intervention with moderate red wine consumption compared to the control group [43]. Other studies have documented an increase in the adipokines leptin and

Table 3
Multivariable-adjusted associations between 1-year changes in urinary tartaric acid (in tertiles) and changes in circulating inflammatory biomarkers (per 1-SD).

		T1 *vs.* T2 β (95% CI per 1SD)	*p*-Value	T1 *vs.* T3 β (95% CI)	*p*-Value	*p*-Trend
sVCAM-1 (ng/mL) *n* = 85	*Model 1*	−0.01 (−0.44; 0.42)	0.955	0.03 (−0.65; 0.71)	0.914	0.917
	Model 2	−0.03 (−0.46; 0.39)	0.844	−0.31 (−0.55; −0.06)	0.025	0.035
sICAM-1 (ng/mL) *n* = 104	*Model 1*	−0.10 (−0.59; 0.39)	0.597	−-0.05 (−0.66; 0.56)	0.825	0.861
	Model 2	−0.31 (−0.52; −0.10)	0.014	−0.29 (−0.52; −0.07)	0.023	0.099
IL-6 (pg/mL) *n* = 161	*Model 1*	0.07 (−0.10; 0.24)	0.311	0.04 (−0.26; 0.33)	0.755	0.761
	Model 2	0.02 (−0.16; 0.20)	0.779	−0.05 (−0.32; 0.21)	0.618	0.598
TNF-α (pg/mL) *n* = 110	*Model 1*	0.04 (−0.15; 0.23)	0.608	0.29 (−0.31; 0.89)	0.267	0.274
	Model 2	0.09 (−0.20; 0.37)	0.469	0.33 (−0.35; 1.01)	0.263	0.269
MCP-1 (pg/mL) *n* = 168	*Model 1*	−0.03 (−0.56; 0.51)	0.901	0.33 (0.01; 0.66)	0.045	0.059
	Model 2	−0.04 (−0.50; 0.43)	0.844	0.36 (−0.19; 0.92)	0.142	0.141

sVCAM-1, soluble vascular cell adhesion molecule-1; sICAM-1, soluble intercellular adhesion molecule-1; IL6, interleukine-6; TNF-α, tumor necrosis factor- α; MCP-1, monocyte chemoattractant protein-1.
β, standardized regression coefficient; CI, confidence interval.
Model 1: sex, age. Model 2: model 1 + physical activity, smoking habit, waist-to-height ratio, intervention group, diabetes, hypercholesterolemia, hypertension, and intake of aspirin and NSAIDs, total energy intake, MedDiet adherence (not considering wine), grapes, and raisins.
All analyses were conducted with robust estimates of the variance to correct for intracluster correlation.
$p < 0.05$ were considered significant.

adiponectin [45–47]. Concerning adhesion molecules VCAM-1 and ICAM-1, evidence suggests that they can decrease after 3 or 4 weeks of wine consumption [18,44]. These findings align with our results, as we identified an inverse association between changes in urinary tartaric acid and plasma sVCAM-1 and sICAM-1 levels after one year of follow-up. ICAM-1 and VCAM-1 function as signalling molecules that promote cell recruitment to the arterial wall, and their circulating levels reflect the degree of endothelial activation caused by CVD risk factors. Indeed, they are considered valuable predictive markers of atherosclerosis [48].

The anti-inflammatory effects of wine consumption could be partially due to its phenolic content. Red wine is a beverage rich in polyphenols such as phenolic acids, flavanols, flavonols, anthocyanins, and resveratrol [49]. *In vivo* studies have demonstrated that red wine polyphenols may have antiatherogenic properties, as they reduce the levels of the adhesion molecules ICAM-1 and VCAM-1 [15,16,50,51]. In humans, polyphenols have exhibited anti-inflammatory effects. In the PREDIMED trial, polyphenol intake was associated with decreased inflammatory biomarkers, including those related to atherosclerosis [25], and urinary polyphenols were shown to be a biomarker of anti-inflammatory diets [52,53]. Polyphenols were also linked to lower plasmatic biomarkers in healthy men, although no changes were observed in cellular adhesion molecules [53]. In addition to the non-alcoholic compounds in wine, the beneficial effects could also be attributed to ethanol, although evidence has yielded inconclusive results. A preclinical study conducted in rats observed that red wine, but not alcohol alone, reduced vascular cell adhesion molecules, oxidative stress, and improved the balance in adipocytokines [51] In humans, Chiva-Blanch et al. found that red wine, dealcoholized red wine, and gin reduced the cellular adhesion molecules, suggesting that the effects could be attributed to both the phenolic compounds and ethanol [54]. A study that combined cross-sectional data of three cohorts and included more than 40,000 participants showed that moderate alcohol intake from different alcoholic beverages was associated with better profiles of inflammatory markers and blood lipids. However, the associations were stronger when alcohol was consumed from wine [55]. On the other hand, Estruch et al. noted a decrease in fibrinogen and interleukin-1 alpha after the wine and gin interventions, but CRP and endothelial adhesion molecules were only reduced with wine [56]. Interestingly, a study comparing red and white wine—both with equal ethanol content but red wine containing higher polyphenol levels—revealed a distinct response in cellular adhesion molecules. While ICAM-1 decreased similarly with both red and white wine, VCAM-1 and E-selectin showed reductions only in response to red wine [44]. In summary, it appears that polyphenols provide wine with an additional anti-inflammatory effect that ethanol alone does not possess.

It is important to emphasize that the advantages of wine consumption are confined to moderate consumption, defined as fewer than 1–2 drinks/day [57]. This aligns with the Mediterranean dietary pattern, where red wine is predominantly enjoyed alongside main meals [22]. Furthermore, it is important to establish different recommendations for wine and alcohol consumption depending on age. There is strong evidence supporting the minimization of alcohol consumption in young individuals because the risks associated with its consumption outweigh the benefits. However, in individuals aged 40 or older, the relative risk of alcohol consumption follows a J-shaped curve, leading us to recommend moderate consumption [58]. Our study's findings are situated within this framework, as participants were older individuals and their consumption fell within these guidelines and showcased adherence to the MedDiet.

The main strength of our study is the application of a biological biomarker, tartaric acid, to evaluate wine consumption. This approach contrasts with less reliable techniques such as food-frequency questionnaires or self-reported surveys. Additionally, the study integrated the use of inflammatory biomarkers, providing a more accurate reflection of participant' status. Furthermore, the study employed a longitudinal design, enabling us to conduct a prospective analysis.

Nonetheless, our study has limitations such as a relatively small sample size and its focus on an older population with a high risk of cardiovascular disease. Furthermore, 24-h urine was not collected due to the study design, which is considered more reliable than spot urine. However, results were adjusted for creatinine levels to account for this variability. In addition, we only examined inflammatory biomarkers most closely associated with atherosclerotic plaques development and did not assess other molecules involved in inflammatory pathways.

In conclusion, our findings support the notion that urinary tartaric acid, identified as a biomarker of wine consumption measured by food-frequency questionnaires, is associated with anti-inflammatory properties related to atherosclerosis in older individuals. Further studies are needed to elucidate the molecular mechanisms behind these associations.

CRediT authorship contribution statement

I.D.L: Conceptualization, Methodology, and Writing – Original Draft. **C.A.R.:** Methodology; **R.C.:** Methodology and Writing – Review & Editing; **P.G.:** Methodology. **M.P.:** Writing – Review & Editing. **M.Á.M.G.:** Writing – Review & Editing. **M.F.:** Writing – Review & Editing; **E.R.:** Writing – Review & Editing. **R.E.:** Conceptualization and Writing – Review & Editing. **R.M.L.R.:** Conceptualization and Writing – Review & Editing.

Data sharing

There are restrictions on the availability of data for the PREDIMED trial, due to the signed consent agreements around data sharing, which only allow access to external researchers for studies following the project purposes. Therefore, data will only be available upon request.

Data described in the manuscript, code book, and analytic code will be made available upon request pending and approval to the PREDIMED trial Steering Committee, only to external researchers for studies following the project purposes.

Funding

This research has been supported by the CICYT [PID2020-114022RB-I00], CIBEROBN from the Instituto de Salud Carlos III, ISCIII from the Ministerio de Ciencia, Innovación y Universidades, NIHgrant “Mediterranean diet, Metabolites, and Cardiovascular Disease” [2R01HL118264-09 and5R01HL118264-08], (AEI/FEDER, UE) and Generalitat de Catalunya (GC) [2017SGR 196] andFIVIN (FB600390). INSA-UB is Maria de Maeztu Unit of Excellence (grant CEX2021-001234-M funded byMICIN/AEI/FEDER, UE). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

E.R. reports grants, personal fees, non-financial support and other from the California Walnut Commission while the study was carried out; grants, personal fees, non-financial support and other from Alexion; and personal fees and other from Amarin, outside the submitted work. R.M.L.-R. reports personal fees from Cerveceros de España, UNIDECO, personal fees, and other from Adventia, Wine in Moderation, Ecoveritas S.A., outside the submitted work. R.E. reports grants from the Fundación Dieta Mediterránea (Spain), and Cerveza y Salud (Spain), and personal fees for given lectures from Brewers of Europe (Belgium), the Fundación Cerveza y Salud (Spain), Pernaud-Ricard (Mexico), Instituto Cervantes (Albuquerque, USA), Instituto Cervantes (Milan, Italy), Instituto Cervantes (Tokyo, Japan), Lilly Laboratories (Spain), and the Wine and Culinary International Forum (Spain), as well as non-financial support for the organization of a National Congress on Nutrition and feeding trials with products from Grand Fountain and Uriach Laboratories (Spain).

Acknowledgments

The PREDIMED trial was supported by the official funding agency for biomedical research of the Spanish government (Instituto de Salud Carlos III) through grants provided to research networks specifically developed for the trial: RTIC G03/140 (Coordinator: R.E.) and RTIC RD 06/0045 (Coordinator: M.A.M.-G.). All investigators of the PREDIMED trial belong to Centro de Investigación Biomédica en Red (CIBER), an initiative of Instituto de Salud Carlos III. I.D.-L. would like to thank the Spanish Ministry of Science Innovation and Universities for the Formación de Profesorado Universitario (FPU20/02478) contract.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2023.100003.

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