ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

ORIGINAL RESEARCH ARTICLE

Effects of redox modulation on postprandial oxy-inflammatory transcriptomic responses in overweight adults with cardiometabolic risk following a Mediterranean diet

Roberto Catanzaro[1], Leila Haghshenas[2,3], Ece Celik Atalay[4], Gulcin Sagdicoglu Celep[5], Aldo Lorenzetti[2], Reza Rastmanesh[2,6], Cristiana Aperio[2], Maki Osato[7], Joseph Cervi[2], and Francesco Marotta[2]*

[1]Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

[2]Regenera International R&D for Aging Intervention, Milano, Italy

[3]Department of Clinical Bioinformatics, Postdoctoral Association, Harvard Medical School, Boston, United States of America

[4]Department of Nutrition and Dietetics, Faculty of Health Sciences, Istanbul Aydın University, Istanbul, Turkiye

[5]Department of Nutrition and Dietetics, Faculty of Health Sciences, Gazi University, Ankara, Turkiye

[6]The Nutrition Society, London, United Kingdom

[7]Osato International Research of Molecular Biology, Gifu, Gifu Prefecture, Japan

***Corresponding author:**
Francesco Marotta
(prof.francescomarotta@gmail.com)

Citation: Catanzaro R, Haghshenas L, Atalay EC, *et al*. Effects of redox modulation on postprandial oxy-inflammatory transcriptomic responses in overweight adults with cardiometabolic risk following a Mediterranean diet. *Eurasian J Med Oncol*. 2026;10(5):026160177. doi: 10.36922/EJMO026160177

Received: April 15, 2026

Revised: June 8, 2026

Accepted: June 11, 2026

Published online: August 20, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract

Introduction: The postprandial phase represents a transient pro-oxidative condition, characterized by an increased vulnerability to oxidative damage following nutrient intake. This state is increasingly recognized as a contributing factor in the early development of atherogenic processes. Alterations in plasma cysteine and glutathione (GSH) redox couples have been shown to correlate with aging and age-related pathologies. Among the principal thiol redox systems regulating plasma redox potential, the reduced cysteine/cystine (CySS) pair predominates, followed by the GSH/oxidized GSH disulfide pair. CySS is considered a marker of systemic oxidative burden, whereas GSH reflects intracellular NADPH-dependent reductive capacity.

Objective: This study aimed to assess both intra- and extracellular redox status during the postprandial period in middle-aged and older sedentary individuals adhering to a Mediterranean dietary pattern, with or without supplementation using a patented fermented papaya preparation (FPP).

Methods: A total of 90 otherwise healthy participants presenting at least one cardiometabolic risk factor were enrolled. Postprandial assessments were conducted at baseline and after three months. Evaluated parameters included inflammatory biomarkers, adhesion molecules, apoptosis in peripheral blood mononuclear cells, and *p53* gene expression.

Results: Compared with the Mediterranean diet alone, three months of FPP supplementation resulted in significant reductions in soluble levels of vascular cell adhesion molecule 1 and intercellular adhesion molecule 1. It also effectively prevented the postprandial increase in Annexin V^+/$DAPI^+$ cells and induced a

protective downregulation of *p53* expression, particularly within the cytoplasmic compartment. Furthermore, CySS concentrations and the CySS:GSH ratio were significantly reduced, while the decline in GSH levels was attenuated under the FPP-supplemented regimen.

Conclusion: These findings support the potential benefit of dietary interventions, particularly when combined with redox-modulating nutraceuticals, in reducing postprandial oxidative stress and its associated metabolically deleterious effects.

Keywords: Postprandial metabolomics; Mediterranean diet; Fermented papaya preparation; Soluble adhesion molecules; p53; Reduced cysteine/cystine/glutathione

1. Introduction

Advancing age is accompanied by progressive dysregulation of cardiovascular and metabolic homeostatic mechanisms, a trajectory amplified by modern lifestyle exposures and associated with escalating vulnerability to chronic pathology.[1,2] A persistent, systemic, low-grade inflammatory milieu represents a central biological feature of aging and is strongly linked to increased disease burden and mortality.[3,4] Immunological aging is typified by a paradoxical state in which basal immune activation remains chronically elevated while the capacity to mount effective responses to new challenges is diminished.[5,6] Substantial evidence identifies chronic inflammation as a principal driver of insulin resistance, type 2 diabetes, cardiovascular pathology, and malignancy, collectively compromising the prospects of healthy aging. In parallel, sustained oxidative stress interacts with inflammatory signaling to accelerate cellular senescence, thereby reinforcing the age-dependent erosion of immune competence.[7,8] Transcriptomic analyses of circulating monocytes in older adults have revealed a reproducible senescence-associated expression signature.[9,10]

The postprandial period is a transient pro-oxidant state characterized by heightened susceptibility to oxidative injury following nutrient intake and is increasingly regarded as an initiating factor in atherogenic processes.[11,12] Oxidative imbalance and chronic inflammation form an interdependent network.[13,14] underlying many disorders prevalent in aging populations, particularly cardiovascular disease.

Reactive oxygen species stimulate innate immune activation, engage redox-responsive cascades such as mitogen-activated protein kinase and nuclear factor kappa B signaling, and enhance the secretion of pro-inflammatory cytokines. Among reactive intermediates, hydroxyl radicals exhibit an especially strong capacity to activate nuclear factor kappa B, a master regulator of inflammatory gene expression.[15] Consumption of lipid-rich meals is known to induce a measurable postprandial disturbance, marked by increased oxidative stress and attenuation of endothelium-dependent vasodilation, which may persist for several hours, even in clinically healthy individuals. Within this context, dietary factors vary in association with the glutathione (GSH)/oxidized GSH (GSSG) and cysteine/cystine (Cys/CySS) redox couples. The GSH and Cys thiol and disulfide systems represent two distinct redox pools and are not in equilibrium in the plasma.[16] The GSH/GSSG couple is more related to tissue redox status, whereas the Cys/CySS couple is more reflective of extracellular oxidation. Thus, given the nonuniformity of dietary correlations with redox pools, the CySS:GSH ratio can be regarded as a robust biomarker of the overall status of redox networks that influence aging and chronic disease. Here, the CySS serves as an indicator of oxidant burden, and GSH reflects the NADPH-reductive capacity within the redox network. This ratio was recently shown to be a stronger predictor of cardiovascular outcomes than the individual "oxy-inflammosome," making it a rational target for preventive and therapeutic strategies, but several food supplements have yielded poor or negative outcomes.[17-23]

The present investigation aimed to evaluate the intra- and extracellular redox systems during the postprandial period under a Mediterranean diet in middle-aged and older sedentary adults following supplementation with a patented fermented papaya preparation (FPP) manufactured by the Osato Research International Institute (FPP®, Patent No. 6401792) or placebo. This functional food is supported by an expanding body of literature documenting redox-modulating and immunoregulatory nutrigenomic properties mediated through key molecular signaling pathways.[24-30]

2. Materials and methods

2.1. Study participants

Eligibility screening was conducted using predefined inclusion and exclusion criteria to enroll 90 appropriate participants. Recruitment focused on otherwise asymptomatic individuals presenting at least one cardiometabolic risk indicator, including: body mass index between 25 and 29 kg/m^2; prehypertension (systolic 120–139 mmHg and/or diastolic 80–89 mmHg) or stage 1 hypertension (systolic 140–159 mmHg and/or diastolic 90–99 mmHg); dyslipidemia defined by fasting triglycerides ≥ 1.7 mmol/L and/or reduced high-density lipoprotein cholesterol (<1.0 mmol/L in men, <1.3 mmol/L in women); fasting plasma glucose ≥ 5.6 mmol/L; or evidence of systemic inflammation indicated by high-sensitivity C-reactive protein ≥ 2.0 mg/L.

2.2. Measurements of vital, anthropometric, and hemodynamic parameters

Vital parameters, including arterial blood pressure and heart rate, were recorded at each study visit, and structured monitoring for adverse events was implemented throughout the protocol. The trial followed a randomized, diet-controlled, placebo-controlled, double-blind crossover design. The study protocol was approved by the Institutional Review Board or Independent Ethics Committee at each participating center.

Anthropometric measurements, body composition, and hemodynamic parameters were collected using standardized procedures. Stature and body mass were recorded to the nearest 0.1 cm and 0.1 kg, respectively, using a calibrated stadiometer and a calibrated scale. Waist girth, along with body composition, was evaluated following established protocols as previously described. Blood pressure and pulse were measured under controlled conditions consistent with American Heart Association guidelines.

Participants were asked to preserve their usual eating patterns, activity levels, and general lifestyle during the trial. The only dietary instruction was to maintain their Mediterranean diet in principle, without altering the caloric load. Individuals taking antihypertensive drugs or lipid-lowering medications were required to maintain their existing prescriptions unchanged for the duration of the study.

2.3. Dietary intake and physical activity monitoring

Subjects were asked to abstain from alcoholic beverages for 15 days before the first intervention (run-in period) and during the study. Natural foods rich in antioxidants were monitored to ensure that individual diets had similar antioxidant content throughout the study.

Participants completed a three-day food diary prior to each study visit to monitor energy and macronutrient intake and to identify potential dietary variations. In addition, a one-day food diary and physical activity log were completed on the day preceding each visit to confirm that they had maintained a sedentary activity pattern. Dietary records were analyzed using a computer-based nutrient analysis program. A baseline three-day food diary was collected before study initiation to assess habitual dietary intake. At the start of the intervention, each participant received a handbook corresponding to their diet. Detailed guidance was provided on which foods to select and avoid when eating out. Intake of sulfur-containing food (fish/seafood, cruciferous vegetables, onions, garlic, and amino acids from dairy and protein intake) was monitored to maintain comparable intake across study periods.

During planned visits, a 24-h dietary recall of the previous day's intake and a short food-use questionnaire specific to the study foods were completed to monitor adherence and reinforce dietary compliance, and Dietsource software (version 2.0) was also used. Additional dietary counseling was provided when either the recall or the questionnaire indicated inadequate adherence. Baseline characteristics of the participants in the study are reported in Table 1.

The trial was carried out in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice. Dietary analysis confirmed that mean macronutrient intake was consistent with a Mediterranean diet pattern (15%, 40–45%, and 35–38% of energy as protein, carbohydrate, and fat [22–24% monounsaturated fatty acid, 8–12% by extra-virgin olive oil, 8–10% saturated fatty acid, and 4% polyunsaturated fatty acid], respectively). Biochemical determinations were performed at entry and at three months. Participants who met all inclusion criteria were randomized using a random number generator in a 1:1 ratio to either a sachet of FPP or a sachet containing dextrose 3 g plus cellulose 1.5 g, administered twice daily (morning and early afternoon). The flow diagram of participant recruitment throughout the study is presented in Figure 1.

Routine biochemical analyses were conducted using a Cobas® analyzer (Roche Diagnostics, Switzerland). In addition, soluble vascular cell adhesion molecule 1 (sVCAM-1) levels were determined through low-cytometric analysis of whole blood samples.

Table 1. Baseline characteristics of the participants

Parameter	Males	Females
Age (years)	64.6 ± 1.7	65.7 ± 1.2
Weight (kg)	88.6 ± 4.5	74.1 ± 2.2*
BMI (kg/m²)	28.21 ± 0.8	27.23 ± 1.1
Waist (cm)	103.5 ± 3.5	89.0 ± 4.4*
Plasma HDL (mmol/L)	1.16 ± 0.05	1.02 ± 0.03
Plasma LDL (mmol/L)	3.07 ± 0.14	2.75 ± 0.15
Plasma TG (mmol/L)	1.21 ± 0.16	0.89 ± 0.18
Plasma ApoB (g/L)	0.91 ± 0.06	0.82 ± 0.04
Plasma ApoA1 (g/L)	1.43 ± 0.03	1.52 ± 0.05
HbA1c (%)	5.4	5.6

Note: Values are reported as means ± standard error, except for HbA1c, which is reported as mean only. *Significantly different from men, $p < 0.05$.
Abbreviations: ApoA1: Apolipoprotein A1; ApoB: Apolipoprotein B; BMI: Body mass index; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides.

At the conclusion of each dietary intervention period, venous blood samples were collected following a 12-h overnight fast. Postprandial samples were obtained two h after food intake using ethylenediaminetetraacetic acid (EDTA)-containing tubes (1 g/L). Immediately after collection, specimens were placed on ice, protected from light, and processed under strictly controlled conditions to minimize exposure to room temperature. Plasma separation was completed within one h by centrifugation at 1,500 × g for 15 min at 4 °C.

2.4. Inflammatory markers and adhesion molecules

Serum concentrations of C-reactive protein were quantified using an enzyme-linked immunosorbent assay method (Biocheck, United States). Plasma levels of sVCAM-1, soluble intercellular adhesion molecule 1 (sICAM-1), and soluble E-selectin (sE-selectin) were measured using commercially available assay kits (R&D Systems, United States). The coefficients of variation were 5.5% for sVCAM-1, 4.4% for sICAM-1, and 7.7% for sE-selectin.

2.5. Plasma thiol–disulfide redox status

Plasma redox parameters were analyzed by high-performance liquid chromatography following the protocol described by Jones and Liang.[30] Briefly, fasting blood samples were collected and immediately mixed with a preservation solution containing borate buffer, iodoacetic

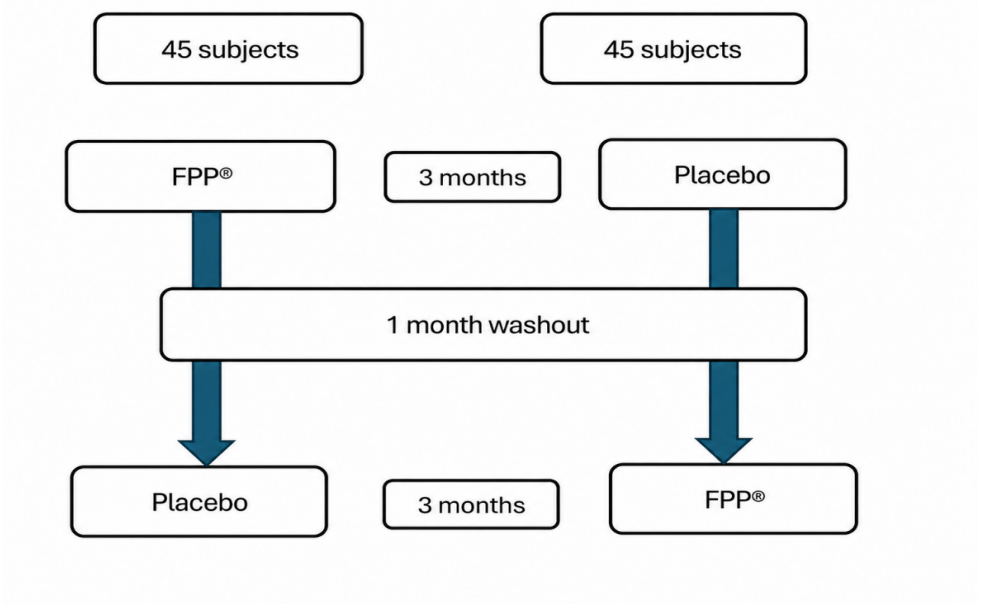


Figure 1. Crossover study design and participant allocation
Abbreviation: FPP: Fermented papaya preparation.

acid, and γ-glutamylglutamate. Samples were stored at −80 °C until analysis. Prior to measurement, derivatization was performed using dansyl chloride to enable fluorescence-based quantification of Cys, CySS, GSH, and GSSG[31] using a high-performance liquid chromatography system (Waters 2690 with autosampler, Waters Corporation, United States). Total GSH levels included both reduced (GSH) and oxidized forms.[32]

2.6. Isolation of peripheral blood mononuclear cells

Peripheral blood mononuclear cells (PBMCs) were obtained from 20 mL of venous blood collected in EDTA tubes. The blood sample was diluted 1:1 with phosphate-buffered saline and gently layered onto Ficoll, then centrifuged in a density gradient at 800×g for 25 min at 20 °C. The mononuclear cell layer was carefully harvested, washed twice with ice-cold phosphate-buffered saline, and resuspended in buffer A (10 mM HEPES, 15 mM KCl, 2 mM $MgCl_2$, 1 mM EDTA). Immediately prior to use, phenylmethylsulfonyl fluoride (1 mM) and dithiothreitol (1 mM) were added. Cell samples were stored at −80 °C until further analysis.

2.7. RNA extraction and quantitative real-time polymerase chain reaction

Total RNA was extracted from PBMCs using a phenol–guanidine-based reagent, following the manufacturer's instructions. RNA concentration was measured using a NanoDrop 1000A spectrophotometer, and RNA integrity was evaluated by agarose gel electrophoresis. Purified RNA samples were stored at −80 °C until further use. To eliminate residual genomic DNA contamination, samples were treated with DNase I (AMPD-1KT, Sigma, United States) prior to reverse transcription.

2.8. Quantitative real-time polymerase chain reaction for gene expression analysis

Gene expression levels were quantified by real-time polymerase chain reaction (PCR) using a Multicolor Real-Time PCR Detection System in combination with iQ SYBR Green Supermix (Bio-Rad Laboratories, United States). Amplification reactions were prepared in a final volume of 20 µL, containing 10 pmol of each primer and 1 µL of first-strand complementary DNA (cDNA) diluted 1:5 (v/v). First-strand cDNA was synthesized from 1 µg of total RNA using a commercially available reverse transcription kit, according to the manufacturer's protocol.

For quantitative PCR analysis, 1 µL of the diluted cDNA (1:5) was used per reaction. Transcript quantification was additionally performed using an OpenArray-based real-time PCR platform with TaqMan probe chemistry. Gene-specific primer and probe assays, validated for human gene expression analysis, were preloaded in duplicate onto OpenArray plates. Thermal cycling conditions consisted of an initial denaturation step at 95 °C for 10 min, followed by 40 cycles of 95 °C for 10 s, 53 °C for 10 s, and 72 °C for 10 s. All samples were analyzed in duplicate, and gene expression levels were normalized to the housekeeping gene *G6PD*, which exhibited lower variability compared to *ACTB*.

2.9. Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences. The results were analyzed using *t*-tests, and significance was set at $p < 0.05$.

3. Results

Routine biochemistry, including liver, kidney, and thyroid function markers, did not change during the study and remained within the reference range (data not shown). In particular, vitamin D3 and zinc levels were within normal limits. The Mediterranean diet, with placebo, did not change adhesion molecule levels; however, the three-month analysis of the tested adhesion molecules showed that the Mediterranean diet did not influence blood levels (Table 2). However, FPP supplementation resulted in a statistically significant reduction in sVCAM-1 and sICAM-1 ($p < 0.05$). These data were not influenced by age or gender (data not shown).

While fasting, the morning proportion of apoptotic cells (Annexin V^+/$DAPI^+$) was within the normal range (not shown); postprandially after the Mediterranean diet in our sedentary and mildly overweight individuals, this biomarker was significantly increased ($p < 0.05$, Figure 2). However, flow cytometric analyses demonstrated that the Mediterranean diet supplemented with FPP was significantly more effective than placebo in preventing this postprandial increase at the three-month follow-up.

In PBMCs, relative *p53* gene expression was associated with a beneficial reduction in postprandial DNA damage, as reflected by a protective downregulation of both nuclear and cytoplasmic *p53* (Figure 3). This effect was significantly more pronounced at the cytoplasmic level in the group receiving co-supplementation with FPP ($p < 0.001$).

Regarding plasma redox markers, CySS concentrations and the CySS:GSH ratio were markedly elevated in untreated overweight participants (body mass index: 25–29.9 kg/m^2) following a Mediterranean diet. Notably, these parameters significantly decreased after switching to an FPP-supplemented dietary regimen. In parallel, this subgroup maintained normal GSH levels, in contrast to the reduced concentrations observed in the placebo-supplemented overweight group (Table 3).

Table 2. Effect of fermented papaya preparation and placebo added to the Mediterranean diet at three months

Variable	Placebo		Fermented papaya preparation		*p*
	Baseline	End	Baseline	End	
sVCAM-1 (ng/mL)	213 ± 11	210 ± 12	208 ± 11	184 ± 12	<0.03*
sICAM-1 (ng/mL)	104 ± 5	106 ± 4	114 ± 5	97 ± 4	<0.02*
sE-selectin (ng/mL)	13 ± 2	14 ± 2	12 ± 2	11 ± 4	n.s.

Abbreviations: sE-selectin: Soluble E-selectin; sICAM-1: Soluble intercellular adhesion molecule 1; sVCAM-1: Soluble vascular cell adhesion molecule 1.

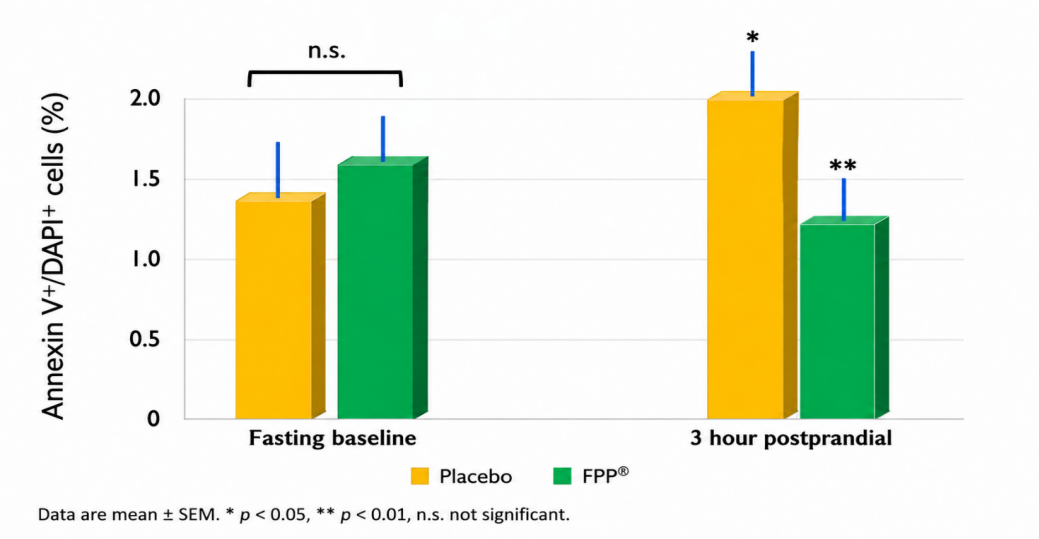


Figure 2. Effect of fermented papaya fermentation on postprandial apoptosis (three months). *$p < 0.05$ vs baseline; ** $p < 0.05$ vs. Mediterranean diet added with placebo.

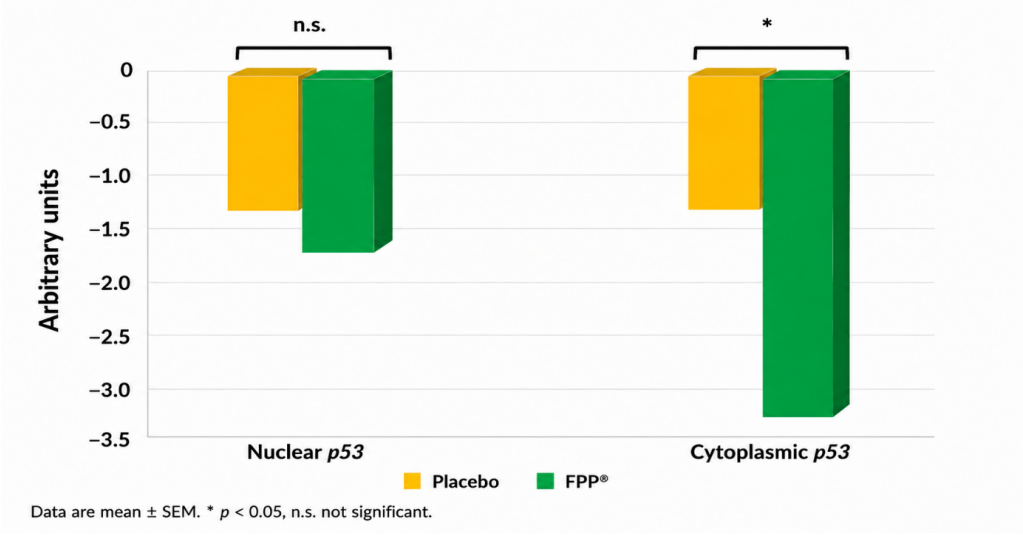


Figure 3. Effect of a placebo or a fermented papaya preparation added to a Mediterranean diet on postprandial *p53*. *$p < 0.05$ vs baseline vs. Mediterranean diet added with placebo.

Table 3. Plasma measures of redox signaling molecules

Parameter	Mediterranean diet + placebo	Mediterranean diet + FPP	*p*
Cys (µmol/L)	9.14 ± 2.05	9.66 ± 2.14	ns
CySS (µmol/L)	93.04 ± 15.26	74.53 ± 19.60	<0.01
GSH (µmol/L)	1.40 ± 0.32	1.85 ± 0.20	<0.01
GSSG (µmol/L)	0.053 ± 0.028	0.050 ± 0.032	ns
CySS/GSH	63.3 ± 12.0	42.3 ± 19.2	<0.01

Abbreviations: Cys: Cysteine; CySS: Cystine; GSH: Reduced glutathione; GSSG: Oxidized glutathione.

4. Discussion

The evaluation of blood transcriptomic changes to assess the early impact of food intake may serve as an *in vivo* cellular model. In this context, dietary exposure alters the circulating environment in which peripheral blood cells operate, eliciting downstream cellular responses that are closely linked to digestive processes and intestinal nutrient absorption, ultimately influencing gene expression profiles.

Given the consumption of multiple meals per day, most individuals remain in a postprandial state for a substantial portion of the day. This sustained postprandial condition has been associated with an increased risk of cardiovascular disease through multiple pathways, while physical activity has been proposed as a potential mitigating strategy.[33,34] Adherence to a Mediterranean dietary pattern has also been linked to reduced thiol-related oxidative stress. Dietary components appear to differentially influence the redox balance of the glutathione (GSH/GSSG) and cysteine (Cys/CySS) systems. These two thiol/disulfide couples represent distinct redox pools that are not in equilibrium within plasma.[35] Specifically, the GSH/GSSG system is more closely associated with intracellular or tissue redox status, whereas the Cys/CySS pair more accurately reflects extracellular oxidative conditions and processes involving cystine uptake and reduction that are independent of GSH reductase activity.[36]

Protein cysteinyl residues located in cellular membranes can undergo reversible oxidation–reduction reactions in response to the extracellular redox environment governed primarily by the Cys/CySS pair, the dominant low-molecular-weight thiol/disulfide system in human plasma.[37]

Although the Mediterranean diet confers well-established health benefits, our findings indicate that sedentary individuals with overweight (but not obesity) exhibit a significant postprandial rise in two soluble adhesion molecules, both recognized as biomarkers of vascular wall inflammation. This response, in association with elevated plasma CySS levels, has been implicated in the pathogenesis of peripheral vascular disease and age-related macular degeneration.[38] Furthermore, an oxidized thiol/disulfide redox state has been observed in conditions characterized by increased carotid intima-media thickness, impaired flow-mediated dilation, and chronic atrial fibrillation.[39,40] Conversely, short-term adherence to a Mediterranean diet in individuals with visceral obesity has shown minimal effects on soluble adhesion molecules.[41] In contrast, supplementation with FPP was associated with normalization of sICAM and sVCAM levels, reductions in plasma CySS concentrations and the CySS/GSH ratio, and an increase in GSH levels.

Overall, compared with the Mediterranean diet alone, the addition of FPP led to an improved CySS:GSH ratio, which has recently been proposed as a stronger predictor of cardiovascular outcomes[42], alongside a reduction in p53-mediated cellular stress responses, a crucial mechanism of DNA protection.[43] Collectively, these findings may provide a basis for strategies to mitigate oxidative stress associated with aging. It is further suggested that a Mediterranean diet enriched with the natural redox-modulating compound FPP could represent a promising approach for managing complex oxidative stress-related conditions, including cardiovascular and neurodegenerative diseases and metabolic disorders[44,45], as well as aging itself. The observed improvements in postprandial physiology following the addition of FPP to an otherwise healthy meal may confer meaningful benefits for vascular function and the reduction of cardiovascular disease risk. Collectively, these findings provide a compelling rationale for advocating dietary modifications—particularly more rigorous adherence to

the Mediterranean diet, potentially enhanced by redox-modulating nutraceuticals —to mitigate oxidative stress.

Although beyond the scope of the present study, these findings may open new avenues for interventional strategies targeting venous thrombosis as well, the third leading cause of cardiovascular mortality worldwide. This condition predominantly affects individuals aged ≥ 45 years, irrespective of underlying abnormalities in the coagulation system. Notably, a recent hypothesis concerning age-related alterations in red blood cells—consistent with our previous observations[24,26] suggests that a prothrombotic activation of red blood cells may occur in middle-aged individuals.[46]

5. Conclusion

Although the randomized crossover design of this study is a strength, some limitations warrant consideration, including the lack of strict patient-to-patient qualitative and quantitative daily dietary calculations and the need for replication in larger, longer-term clinical trials. Consequently, the reported findings should be interpreted with caution. In addition, inflammatory status was assessed exclusively through circulating adhesion molecules and PBMC apoptosis. Finally, because many adults spend much of the day in the postprandial state, protection against oxidative damage is increasingly relevant for reducing the risk of chronic disease.

Acknowledgments

The authors gratefully acknowledge Mr. Yuki Hayashi for his long-standing role as an inspiring advocate and visionary in the field of health.

Funding

Dr. Maki Osato runs a lab supported by the Osato International Foundation as part of its not-for-profit social and cultural initiatives and receives no benefits from commercial activities.

Conflict of interest

M. Osato is affiliated with Osato International Research of Molecular Biology, which is associated with the fermented papaya preparation evaluated in this study. The remaining authors declare no conflicts of interest.

Author contributions

Conceptualization: Roberto Catanzaro, Francesco Marotta
Formal analysis: Leila Haghshenas, Ece Celik Atalay, Reza Rastmanesh, Joseph Cervi
Investigation: Aldo Lorenzetti, Cristiana Aperio, Francesco Marotta,
Methodology: Leila Haghshenas, Gulcin Sagdicoglu Celep, Maki Osato, Joseph Cervi
Writing–original draft: Ece Celik Atalay, Cristiana Aperio, Francesco Marotta
Writing–review & editing: Aldo Lorenzetti, Maki Osato, Francesco Marotta

Ethics approval and consent to participate

This study was carried out in compliance with the Good Clinical Practice guidelines and approved by the Internal Ethics Committee (number: FF-273-April-22-2025) of the San Babila Clinic, Corso Matteotti, 1, Milano. Verbal consent was obtained from each subject to participate in the study.

Consent for publication

Not applicable.

Availability of data

Data will be made available upon reasonable request to the corresponding author.

References

1. Hu C, Zhang X, Teng T, Ma ZG, Tang QZ. Cellular Senescence in Cardiovascular Diseases: A Systematic Review. *Aging Dis*. 2022;13(1):103-128.

   doi: 10.14336/AD.2021.0927

2. Regitz-Zagrosek V, Lehmkuhl E, Mahmoodzadeh S. Gender aspects of the role of the metabolic syndrome as a risk factor for cardiovascular disease. *Gend Med*. 2007;4 Suppl B:S162-177.

   doi: 10.1016/s1550-8579(07)80056-8

3. Pérez-Castillo IM, Rueda R, Bouzamondo H, *et al.* Does Lifelong Exercise Counteract Low-Grade Inflammation Associated with Aging? A Systematic Review and Meta-Analysis. *Sports Med*. 2025;55(3):675-696.

   doi: 10.1007/s40279-024-02152-8

4. Baechle JJ, Chen N, Makhijani P, *et al.* Chronic inflammation and the hallmarks of aging. *Mol Metab*. 2023;74:101755.

   doi: 10.1016/j.molmet.2023.101755

5. An aged immune system drives senescence and ageing of solid organs. *Nature*. 2021;594(7861):100-105.

   doi: 10.1038/s41586-021-03547-7

6. Cisneros B, García-Aguirre I, Unzueta J, *et al.* Immune system modulation in aging: Molecular mechanisms and therapeutic targets. *Front Immunol*. 2022;13:1059173.

   doi: 10.3389/fimmu.2022.1059173

7. Xu W, Wong G, Hwang YY, Larbi A. The untwining of

immunosenescence and aging. *Semin Immunopathol*. 2020;42(5):559-572.

doi: 10.1007/s00281-020-00824-x

8. Lewkiewicz S, Chuang YL, Chou T. A Mathematical Model of the Effects of Aging on Naive T Cell Populations and Diversity. *Bull Math Biol.* 2019;81(7):2783-2817.

doi: 10.1007/s11538-019-00630-z

9. Ahmed B, Si H. The Aging of Adipocytes Increases Expression of Pro-Inflammatory Cytokines Chronologically. *Metabolites*. 2021;11(5):292.

doi: 10.3390/metabo11050292

10. Huang Z, Chen B, Liu X, *et al.* Effects of sex and aging on the immune cell landscape as assessed by single-cell transcriptomic analysis. *Proc Natl Acad Sci USA*. 2021;118(33):e2023216118.

doi: 10.1073/pnas.2023216118

11. Yanai H, Adachi H, Hakoshima M, Katsuyama H. Postprandial Hyperlipidemia: Its Pathophysiology, Diagnosis, Atherogenesis, and Treatments. *Int J Mol Sci*. 2023;24(18):13942.

doi: 10.3390/ijms241813942

12. de Vries MA, Klop B, Eskes SA, *et al.* The postprandial situation as a pro-inflammatory condition. *Clin Investig Arter.* 2014;26(4):184-192.

doi: 10.1016/j.arteri.2014.02.007

13. Le NA. Lipoprotein-associated oxidative stress: a new twist to the postprandial hypothesis. *Int J Mol Sci*. 2014;16(1):401-419.

doi: 10.3390/ijms16010401

14. Lacroix S, Rosiers CD, Tardif JC, Nigam A. The role of oxidative stress in postprandial endothelial dysfunction. *Nutr Res Rev*. 2012;25(2):288-301.

doi: 10.1017/S0954422412000182

15. Srivastava SP, Kopasz-Gemmen O, Thurman A, *et al.* The molecular determinants regulating redox signaling in diabetic endothelial cells. *Front Pharmacol*. 2025;16:1563047.

doi: 10.3389/fphar.2025.1563047

16. Jones DP. Redefining oxidative stress. *Antioxid Redox Signal*. 2006;8(9-10):1865-1879.

doi: 10.1089/ars.2006.8.1865

17. Altıparmak IH, Erkuş ME, Sezen H, *et al.* The relation of serum thiol levels and thiol/disulphide homeostasis with the severity of coronary artery disease. *Kardiol Pol.* 2016;74(11):1346-1353.

doi: 10.5603/KP.a2016.0085

18. Mankowski RT, You L, Buford TW, *et al.* Higher dose of resveratrol elevated cardiovascular disease risk biomarker levels in overweight older adults - A pilot study. *Exp Gerontol*. 2020;131:110821.

doi: 10.1016/j.exger.2019.110821

19. Joris PJ, Plat J, Bakker SJ, Mensink RP. Effects of long-term magnesium supplementation on endothelial function and cardiometabolic risk markers: A randomized controlled trial in overweight/obese adults. *Sci Rep*. 2017;7(1):106.

doi: 10.1038/s41598-017-00205-9

20. Pathak S, Kesavan P, Banerjee A, *et al.* Metabolism of Dietary Polyphenols by Human Gut Microbiota and Their Health Benefits. In: *Polyphenols: Mechanisms of Action in Human Health and Disease*. Kidlington, UK: Elsevier; 2018:347-359.

doi: 10.1016/b978-0-12-813006-3.00025-8

21. Ambagaspitiya SS, Appuhamillage GA, Wimalawans VC, *et al.* Supplementation with Resveratrol and Curcumin Does Not Affect the Inflammatory Response to a High-Fat Meal in Older Adults with Abdominal Obesity: A Randomized, Placebo-Controlled Crossover Trial. *J Nutr*. 2018;148(3):379-388.

doi: 10.1093/jn/nxx072

22. Teunissen-Beekman KF, Dopheide J, Geleijnse JM, *et al.* Dietary proteins improve endothelial function under fasting conditions but not in the postprandial state, with no effects on markers of low-grade inflammation. *Br J Nutr*. 2015;114(11):1819-1828.

doi: 10.1017/S0007114515003530

23. Morand C, Dubray C, Milenkovic D, *et al.* Hesperidin contributes to the vascular protective effects of orange juice: a randomized crossover study in healthy volunteers. *Am J Clin Nutr.* 2011;93(1):73-80.

doi: 10.3945/ajcn.110.004945

24. Marotta F, Safran P, Tajiri H, *et al.* Improvement of hemorheological abnormalities in alcoholics by an oral antioxidant. *Hepatogastroenterology*. 2001;48(38):511-517.

25. Tomella C, Catanzaro R, Illuzzi N, *et al.* The hidden phenomenon of oxidative stress during treatment of subclinical-mild hypothyroidism: a protective nutraceutical intervention. *Rejuvenation Res*. 2014;17(2):180-183.

doi: 10.1089/rej.2013.1495

26. Marotta F, Pavasuthipaisit K, Yoshida C, Albergati F, Marandola P. Relationship between aging and susceptibility of erythrocytes to oxidative damage: in view of nutraceutical interventions. *Rejuvenation Res*. 2006; 9(2):227-230.

doi: 10.1089/rej.2006.9.227

27. Marotta, F, Koike K, Lorenzetti A, *et al.* Regulating redox balance gene expression in healthy individuals by nutraceuticals: a pilot study. *Rejuvenation Res*. 2010;13(2-3):175-178.

doi: 10.1089/rej.2009.0950

28. Bertuccelli G, Zerbinati N, Marcellino M, *et al.* Effect of a quality-controlled fermented nutraceutical on skin aging markers: An antioxidant-control, double-blind study. *Exp Ther Med*. 2016;11(3):909-916.

doi: 10.3892/etm.2016.3011

29. Marotta F, Chui DH, Jain S, *et al.* Effect of a fermented nutraceutical on thioredoxin level and TNF-alpha signalling in cirrhotic patients. *J Biol Regul Homeost Agents*. 2011;25(1):37-45.

30. Jones DP, Liang Y. Measuring the poise of thiol/disulfide couples in vivo. *Free Radic Biol Med*. 2009;47(10):1329-1338.

doi: 10.1016/j.freeradbiomed.2009.08.021

31. Guzonjić A, Crevar M, Simić I, *et al.* Alterations in GSH/GSSG and CyS/CySS redox status in small cell lung cancer patients undergoing chemotherapy. *Discov Oncol*. 2025;16(1):1445.

doi: 10.1007/s12672-025-03251-2

32. Bellini A, Nicolò A, Bazzucchi I, Sacchetti M. Effects of Different Exercise Strategies to Improve Postprandial Glycemia in Healthy Individuals. *Med Sci Sports Exerc*. 2021;53(7):1334.

doi: 10.1249/MSS.0000000000002607

33. Solomon TPJ, Eves FF, Laye MJ. Targeting Postprandial Hyperglycemia With Physical Activity May Reduce Cardiovascular Disease Risk. But What Should We Do, and When Is the Right Time to Move? *Front Cardiovasc Med*. 2018;5:99.

doi: 10.3389/fcvm.2018.00099

34. Henson J, Davies MJ, Bodicoat DH, *et al.* Breaking Up Prolonged Sitting With Standing or Walking Attenuates the Postprandial Metabolic Response in Postmenopausal Women: A Randomized Acute Study. *Diabetes Care*. 2016;39(1):130-138.

doi: 10.2337/dc15-1240

35. Dong Y, Sameni S, Digman MA, Brewer GJ. Reversibility of Age-related Oxidized Free NADH Redox States in Alzheimer's Disease Neurons by Imposed External Cys/CySS Redox Shifts. *Sci Rep*. 2019;9(1):11274.

doi: 10.1038/s41598-019-47582-x

36. Watson WH, Burke TJ, Zelko IN, Torres-González E, Ritzenthaler JD, Roman J. Differential Regulation of the Extracellular Cysteine/Cystine Redox State (EhCySS) by Lung Fibroblasts from Young and Old Mice. *Oxid Med Cell Longev*. 2016;2016:1561305.

doi: 10.1155/2016/1561305

37. Dong WC, Guo JL, Xu L, *et al.* Impact of homocysteine on acute ischemic stroke severity: possible role of aminothiols redox status. *BMC Neurol.* 2024;24(1):175.

doi: 10.1186/s12883-024-03681-5

38. Moriarty-Craige SE, Ha KN, Sternberg P Jr, *et al.* Effects of long-term zinc supplementation on plasma thiol metabolites and redox status in patients with age-related macular degeneration. *Am J Ophthalmol*. 2007;143(2):206-211.

doi: 10.1016/j.ajo.2006.09.056

39. Goudev A, Kyurkchiev S, Gergova V, *et al.* Reduced Concentrations of Soluble Adhesion Molecules after Antioxidant Supplementation in Postmenopausal Women with High Cardiovascular Risk Profiles – A Randomized Double-Blind Study. *Cardiology*. 2000;94(4):227-232.

doi: 10.1159/000047322

40. Rallidis LS, Kolomvotsou A, Lekakis J, *et al.* Short-term effects of Mediterranean-type diet intervention on soluble cellular adhesion molecules in subjects with abdominal obesity. *Clin Nutr ESPEN*. 2017;17:38-43.

doi: 10.1016/j.clnesp.2016.11.002

41. Ishinoda Y, Masaki N, Hitomi Y, *et al.* Effectiveness of the serum ratio of l-cysteine to glutathione for the prediction of cardiovascular events. *J Clin Biochem Nutr*. 2025;77(2):174-181.

doi: 10.3164/jcbn.24-156

42. Potere N, Bonaventura A, Abbate A. Novel Therapeutics and Upcoming Clinical Trials Targeting Inflammation in Cardiovascular Diseases. *Arter Thromb Vasc Biol*. 2024;44(12):2371-2395.

doi: 10.1161/ATVBAHA.124.319980

43. Miller KN, Li B, Pierce-Hoffman HR, *et al.* p53 enhances DNA repair and suppresses cytoplasmic chromatin fragments and inflammation in senescent cells. *Nat Commun*. 2025;16(1):2229.

doi: 10.1038/s41467-025-57229-3

44. Diekmann C, Huber H, Preuß M, *et al.* Moderate Postmeal Walking Has No Beneficial Effects Over Resting on Postprandial Lipemia, Glycemia, Insulinemia, and Selected Oxidative and Inflammatory Parameters in Older Adults with a Cardiovascular Disease Risk Phenotype: A Randomized Crossover Trial. *J Nutr*. 2019;149(11):1930-1941.

doi: 10.1093/jn/nxz148

45. Catanzaro R, Calabrese F, Occhipinti S, *et al.* Nonalcoholic fatty liver disease increases risk for gastroesophageal reflux symptoms. *Dig Dis Sci*. 2014;59(8):1939-1945.

doi: 10.1007/s10620-014-3113-7

46. Chauhan W, Sj S, Ferdowsi S, Sohel A, Zennadi R. Red blood cell Rpl13a small noncoding nucleolar RNAs guides 2'-O-methylation on peroxidasin messenger RNA promoting venous thrombosis in aging. *J Thromb Haemost*. 2025.

doi: 10.1016/j.jtha.2025.02.036