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Testing a patented fermented papaya preparation on key aging redox and functional markers in middle-aged individuals. A 10-month randomized, single-blind, crossover study

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Submission Date: October 22nd, 2025; **Acceptance Date:** November 18th, 2025; **Publication Date:** November 25th, 2025

Please cite this article as: Cervi J., Catanzaro R., Rastmanesh R., Marotta F., Castillo-Garzon M., Osato M., Nardin A., Aperio C., Moghadam Ahmadi A. Testing a patented fermented papaya preparation on key aging redox and functional markers in middle-aged individuals. A 10-month randomized, single-blind, crossover study. *Bioactive Compounds in Health and Disease* 2025; 8(11): 505 – 516. DOI: https://doi.org/10.31989/bchd.v8i11.1818

ABSTRACT

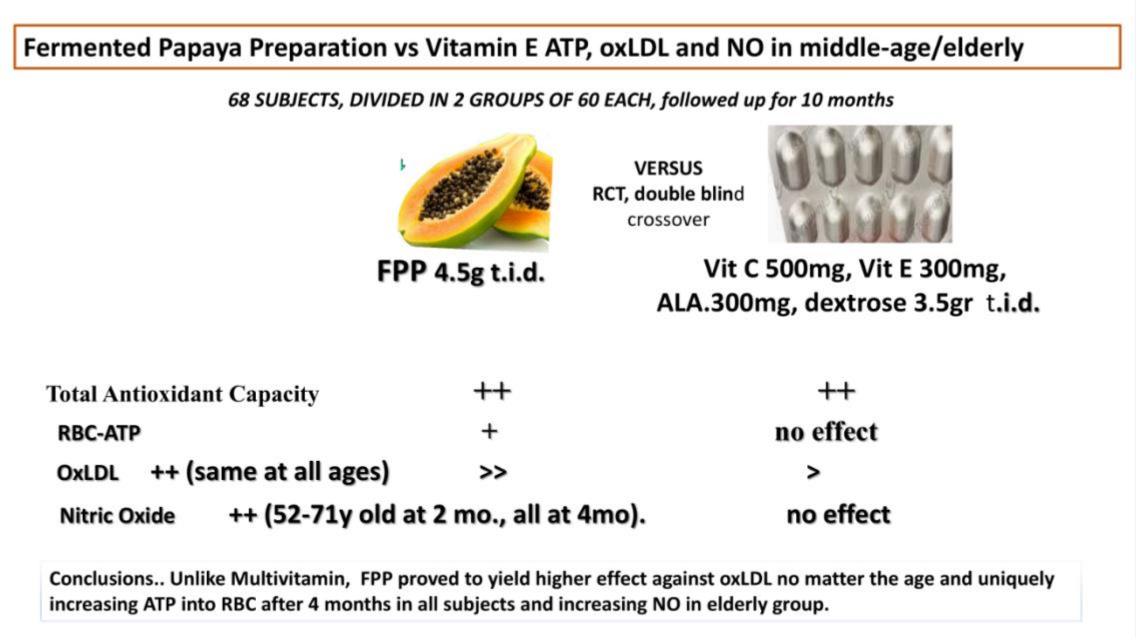
Objectives: Physical activity and cardiovascular system efficiency are known to be inversely associated with all-cause mortality. Thus, efforts are focused on preventative strategies for middle-aged and elderly subjects who lead sedentary lifestyles and may be further burdened. This is associated with a decay in mitochondrial efficiency and capacity for adenosine triphosphate (ATP) production, which is associated with decreased performance and overall bioenergetics.

Methods: After having confirmed their eligibility, 160 (45-72 years old, m/f: 50/110 participants were admitted into a double blind, 4-month crossover, separated by a one-month washout period, trial, and random assignment to one of two study treatments using a patented fermented papaya preparation (FPP®), endowed with antioxidant properties. Subjects took two sachets per day, each one containing synthetic vitamins (Vitamin C, Vitamin E, alpha-lipoic acid, and dextrose). At the beginning, 1, 2, and 4 months, biochemical assays of oxidized LDL (oxLDL) and nitric oxide (NO) were performed on peripheral blood plasma or red blood cells (RBC) (ATP) on sample aliquots stored at −80°C.

Results: FPP® intervention showed a statistically significant increase in RBC-ATP (0.05 vs Multivitamin) at 2 and 4 months of observation. Both treatments significantly improved Total Antioxidant Capacity (TAC) at the 4-month observation with an earlier 2-month increase in the FPP® group ($p<0.01$). Despite an overall wide scattering of OxLDL values, by clustering the 52-71-year-old participants, this group has significantly higher values than the younger counterpart. Both treatments, particularly FPP® (expressed as percentage change from baseline), led to a significant decrease ($p<0,05$). While Multivitamin treatment was ineffective in improving FMD or NO levels, these parameters significantly increased during FPP® treatment.

Conclusion: The present research study shows that a specific fermented functional food (FPP®) may offer an interesting interventional strategy to tentatively counteract age-related endothelial dysfunction, redox dysregulation, and bioenergetic decline, compared with a synthetic multivitamin mixture.

Keywords: Fermented papaya, aging redox, endothelial dysfunction, redox dysregulation, bioenergetic decline



Fermented Papaya Preparation vs Vitamin E ATP, oxLDL and NO in middle-age/elderly

68 SUBJECTS, DIVIDED IN 2 GROUPS OF 60 EACH, followed up for 10 months

VERSUS
RCT, double blind
crossover

FPP 4.5g t.i.d.

Vit C 500mg, Vit E 300mg, ALA.300mg, dextrose 3.5gr t.i.d.

Total Antioxidant Capacity	++	++
RBC-ATP	+	no effect
OxLDL ++ (same at all ages)	>>	>
Nitric Oxide ++ (52-71y old at 2 mo., all at 4mo).		no effect

Conclusions.. Unlike Multivitamin, FPP proved to yield higher effect against oxLDL no matter the age and uniquely increasing ATP into RBC after 4 months in all subjects and increasing NO in elderly group.

Graphical Abstract: Blueberries and raspberries as endocrine modulators: mechanisms, clinical evidence, and translational guidance.

INTRODUCTION

Aging is associated with decreased physiological function and reduced stress-resilience mechanisms [1]. This contributes to an increased risk for developing chronic diseases such as cardiovascular disease, diabetes, cancer, and neurodegenerative diseases. Thus, targeting molecular processes of aging will enable healthier, longer lives and lower social and family burdens [2-4]. This has raised fundamental thoughts [5]. Undoubtedly, physical activity [6] and cardiovascular health status are inversely associated with all-cause mortality, underscoring the importance of prioritizing these factors in prevention strategies for middle-aged and elderly subjects [7]. Natural supplements have also been used in trials to mitigate age-related and menopausal mitochondrial functional decline [8-9]. Moreover, it has been reported that the decay in mitochondrial efficiency and capacity for adenosine triphosphate (ATP) production is associated with decreased performance and increased fatigue [10]. In addition, very recent data show a lack of bioenergetic muscular plasticity in the elderly, who are unable to switch to increased non-oxidative ATP production and instead rely on higher oxidative ATP production [11]. Increased oxidative stress with the aging process or cardiovascular disease, specifically in sedentary individuals, shows a defective nitric oxide (NO) bioavailability in the systemic circulation [12]. Interestingly, while NO donors such as organic nitrates are not advisable because they may favor endothelial dysfunction [13] and potentially trigger rapid tachyphylaxis, in recent years, NO production via fruit fermentation technologies has gained supporters [14-17]. Fermented Papaya Preparation (FPP®) is a patented, batch-controlled 10-month fermentation compound endorsed by multiple in vitro and clinical papers, as well as by Quantitative Structure-Activity Relationship (QSAR) analysis for its antioxidant and immune-modulating properties [18-22]. In a previous study on the skin, we unveiled that FPP®, other than more evident effects on antioxidant parameters, could also mildly, albeit significantly, increase the concentration of NO [23]. Although FPP contains small amounts of arginine, a known precursor of NO, its observed tissue increase noted in the study was probably an indirect effect of its powerful redox balance signaling. This study aimed to test this fermented functional food in generally healthy individuals of different ages for possible effects on erythrocyte (RBC) ATP content, oxidized-LDL, total antioxidant capacity, and endothelial function as compared to a wide range of antioxidant formulas.

Population selection: Exclusion criteria: Body Mass Index (BMI) ≥ 39, subject having experienced any main acute cardiovascular event in the last 12 months, antibiotic use within 4 weeks of randomization, significant use of lipid-lowering drugs, antacids, corticosteroids, or sex hormones. Participants with substance abuse problems are defined as: Use of recreational drugs or nicotine/caffeine dependence, high-risk drinking as defined by consumption of 4 or more alcohol-containing beverages on any day or eight or more alcohol-containing beverages per week. Participants with uncompensated thyroid disorders. Patients who have clinically significant impairment following severe illness (i.e., endocrine system, immune system, respiratory system, hepatobiliary system, kidney, neuropsychiatric, tumors, chronic gastrointestinal diseases, etc.). Patients taking health functional foods or herbal medicines with HmGCoA inhibitory properties, weight loss meds, etc (such as plant sterols, n-3 fatty acids, and soya protein) within the last 3 months before screening as well as vital signs outside of acceptable range at the screening Visit: blood pressure >159/99, oral temperature ≥ 37.5°, resting pulse >100b/m.

This study complied with the principles outlined in the Declaration of Helsinki and the guidelines for Biomedical Research. Before the study entry, written informed consent was obtained from all 120 participants (Figure 1). They were asked not to make any changes to their diet or lifestyle. Four visits were set, at baseline, 1 month, 2 months, and 4 months. Subjects were free to stop treatment at any time. Adverse events (AEs) were recorded and appropriately coded.

Once the medical examination had confirmed their eligibility, the participants were admitted into the crossover trial (Figure 1) and randomly assigned to one of two study treatments using randomly generated numbers as followed: FPP® two sachets per day or two sachets, each one containing synthetic vitamins such as: Vitamin C 500 mg, Vitamin E 300 mg, alpha-lipoic acid 300mg, dextrose 5g. The sachet of the Multivitamin was slightly heavier to allow for the 5 grams of dextrose needed to mitigate the pungent flavor of its content.

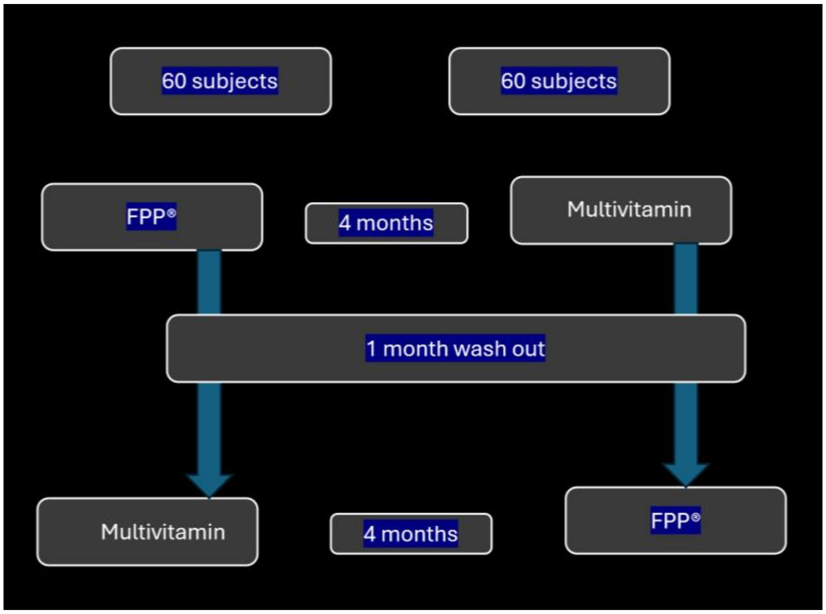


Figure 1. Research flowchart

Participants in the study were unaware of their treatment assignments: Subjects received the exact number of sachets (made anonymous by a white tape applied on top) required for each intervention period, and they were asked to return all unused sachets. Compliance was measured midway through each intervention period during an interview and at the end of each period. A subject was considered compliant when he/she consumed ≥90% of the sachets provided.

METHODS

Diet and Anthropometry Assessments: Dietary intake was assessed using 3-day weighed collection data collected by subjects' self-record at baseline between visits.

BMI was determined by anthropometry, and arterial systolic and diastolic blood pressures were assessed in triplicate using a sphygmomanometerat the end of each visit.

Questionnaires were also completed by an experienced nutritionist on each occasion, including the 14-item Mediterranean Diet Adherence Screening (MEDAS) questionnaire.

Pre-visit standardization and blood collection: Participants arrived in the morning after an overnight fast (~12 h) with water permitted and having avoided caffeine, alcohol, and vigorous activity for 24 h. Venous blood was drawn into BD Vacutainer tubes (BD Biosciences, San Jose, CA, USA) containing: 3.2% buffered sodium citrate (for whole-blood hemostasis and flow-cytometry assessments), EDTA (for plasma nitrate analyses), or lithium heparin (for plasma nitrite analyses). For plasma workups, samples were centrifuged at 1,500 × g for 10 min at 22 °C within 3 min of collection. Plasma was aliquoted, snap-frozen in liquid nitrogen, and stored at −80 °C until assay.

Nitric oxide–related measures: Plasma NOx was quantified using a Griess-based colorimetric assay (R&D Systems, Minneapolis, MN, USA). Samples were run in triplicate, and optical density was read at 540 nm on an xMark microplate spectrophotometer (Bio-Rad, Hercules, CA, USA). In a subset, NO (µmol/L) was also determined using a kit based on the Griess reaction chemistry (Active Motif, Rixensart, Belgium).

Erythrocyte nucleotides: ATP, ADP, and AMP were measured in whole blood and converted to intra-erythrocyte concentrations (µmol/L RBC) using duplicate hematocrit values obtained by the standard microhematocrit method. This calculation assumes negligible nucleotide content in plasma due to nucleotidase activity.

ATP assay (bioluminescence): Polymorphonuclear (PMN) pellets (100 µL) were kept on ice before processing. Ice-cold water (990 µL) was added to the pellet (10 µL) to lyse cells on ice. ATP was quantified with a luciferin–luciferase bioluminescence kit following the manufacturer's instructions. Briefly, luciferase consumes ATP while catalyzing the oxidation of D-luciferin to an excited intermediate that emits light upon returning to the ground state; with ATP as the limiting reagent, light output is proportional to ATP content. Chemiluminescence was recorded on a Victor2 1420 multilabel counter with Wallac 1420 Software (Perkin Elmer, Waltham, MA, USA). Results are expressed in mmol/L (mM).

Total antioxidant capacity (TAC): TAC was determined by photochemiluminescence using the Photochem instrument (Analytik Jena, Jena, Germany) and the ACL reagent kit with Trolox standards. In brief, 200 µL plasma was mixed with 200 µL dH_2O and 400 µL ethanol; 800 µL hexane was then added, the mixture shaken for 1 min, and centrifuged at 1,000 × g for 5 min. The lipid phase (200 µL) was collected, dried under nitrogen, stored at −80 °C, reconstituted in 200 µL methanol, and centrifuged at 5,000 × g for 1 min. Supernatants were analyzed per the Photochem application note. TAC was calculated using the kit's calibration approach (Trolox equivalents).

Lipid peroxidation (TBARS): TBARS were assessed spectrophotometrically as an index of lipid peroxidation. To minimize interference, trichloroacetic acid was used to precipitate proteins before color development.

Oxidized LDL (oxLDL): Plasma oxLDL was measured by ELISA (Mercodia, Uppsala, Sweden; Mercodia Inc., USA) using a direct sandwich format with two monoclonal antibodies recognizing distinct epitopes on oxidized apoB. The detection limit was 0.5 mU/L.

Vascular function — flow-mediated dilation (FMD): Endothelium-dependent brachial artery FMD was assessed in the morning session after the standardized fast and abstentions noted above; participants were instructed to avoid vasoactive substances and exercise. The right brachial artery was imaged 2–3 cm proximal to the antecubital fossa using a 12-MHz linear-array Doppler probe at an insonation angle < 60°. The baseline diameter was recorded, and a forearm cuff was inflated to 250 mmHg for 5 min to induce reactive hyperemia. Longitudinal images were captured 30 s before and for 2 min after cuff deflation. FMD% was calculated as:

$$FMD\% = \frac{peak\ diameter - baseline\ diameter}{baseline\ diameter} \times 100.$$

Statistics: Analyses followed a modified intent-to-treat framework, including randomized participants with complete baseline data (n = 149). Data are presented as mean ± SD—two-sided α = 0.05 defined statistical significance. Variables with non-normal distributions (as assessed by standard probability plots) were log-transformed before analysis. Baseline between-group differences were evaluated using independent-samples t-tests on transformed data when appropriate, and chi-square tests for categorical variables.

RESULTS

Adherence. Participants in both interventional groups completed 3-d food analyses at baseline and at 1, 2, and 4 months. Data were entered into FoodWorks Professional software (Version 7.0.3016; Software), and the mean daily intake of foods was calculated. No drop-off or meaningful side effects were reported (2 male subjects in Multivamin treatment reported episodic, slight nocturia). Three female subjects in the FPP® group and one in the Multivitamin group who had halted melatonin supplementation by protocol reported minor insomnia or early awakening. Routine biochemistry was unaltered throughout the study period. Seven subjects in each treatment group who had mild untreated lipid disorders returned to values within the range already at the second month of control, regardless of age or gender.

Baseline RBC-ATP levels in both groups were comparable and unaffected by age. During the nutraceutical intervention, a comparable, non-significant trend increase (Figure 2) occurred in both groups at the 1-month observation. This yielded a statistically significant increase in the FPP® group (0.05 vs Multivitamin) at 2 and 4 months of observation.

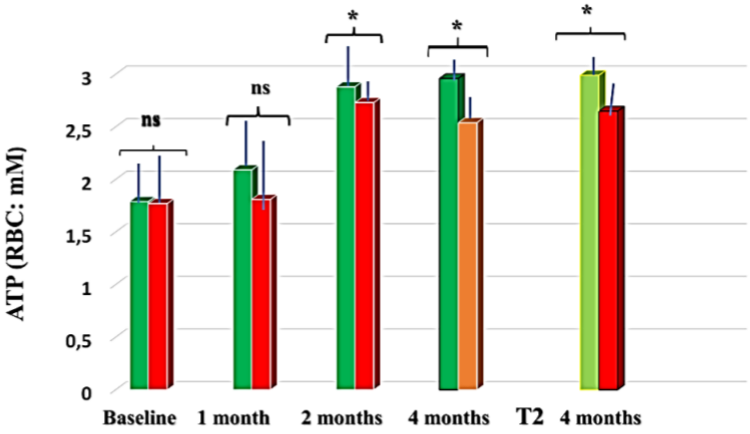


Figure 2. Effect of FPP and multivitamin on time- course RBC-ATP. Green bars: FPP®, red bars: Multivitamin, ns: not statistically significant.

A time-course modification in TAC was observed during treatment with FPP® or Multivitamin (Table 1). Both treatments yielded a statistically significant improvement of TAC (p<0,05). Unlike Multivitamin, the FPP® effect was evident after only 2 months of treatment. No specific age-related changes were observed, although subjects aged 68 years or older showed a non-significant lower baseline value in both groups (FPP®: 736.2 ± 98.4; Multivitamin: 763.1 ± 92.59). No gender difference was observed, regardless of treatment.

Table 1. Effect of FPP® and Multivitamin on TAC plasma values over 4 months of treatment.

TAC (mmol/L)	**Baseline**	**1 month**	**2 months**	**4 months**	**p value**
FPP®	809.2 ± 91.2	829.1 ± 87.4	912.7 ± 87.2*	915.2 ± 92.2 *	<0.01
Multivitamin	812.4 ± 78.8	824.4 ± 98.3	833.2 ± 77.5 *	908.2 ± 77.8 *	<0.01

Plasma Oxidized LDL (oxLDL) values showed wide dispersion, primarily due to age, with values in healthy, physically active subjects aged below 54 comparable to those of younger adults (separate 25-46 years of age, data not shown). However, both males and females in their 55-72 years of age, starting from 2 months, a statistically decreased plasma concentration of circulating marker of lipid oxidative stress, in the range of 16% and 12% in FPP and Multivitamin, respectively (both p<0.05 vs baseline, no significant difference among treatments in Figures 3a and 3b).

Figure 3a. shows plasma oxidized LDL (percentage change values) under the two different nutraceutical treatments. Both treatments resulted in a comparable decrease in this parameter in the 52-72-year age cohort (p<0.05 vs baseline) at 2 months of study. Still, FPP yielded the best data at 4 months, expressed as percent change (p<0,05 vs Multivitamin).

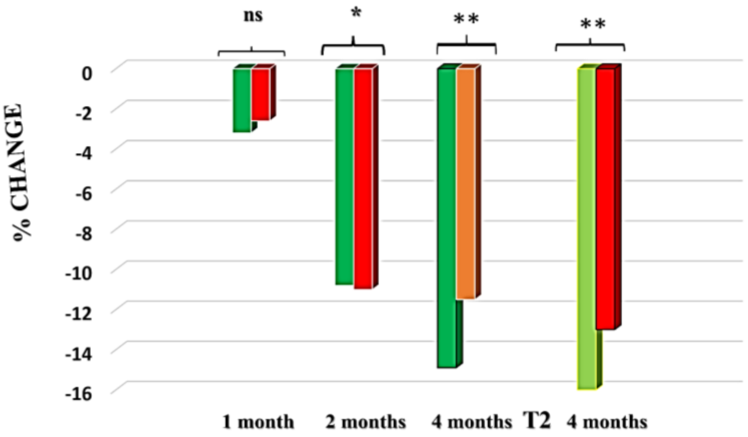


Figure 3 A. Centage change of oxidized lDL: Effect of FPP and multivitamin (55-72 years): Green bars: FPP®, red bars: Multivitamin, ns: not statistically significant. *p<0.05 vs baseline; **p<0.05 vs Multivitamin

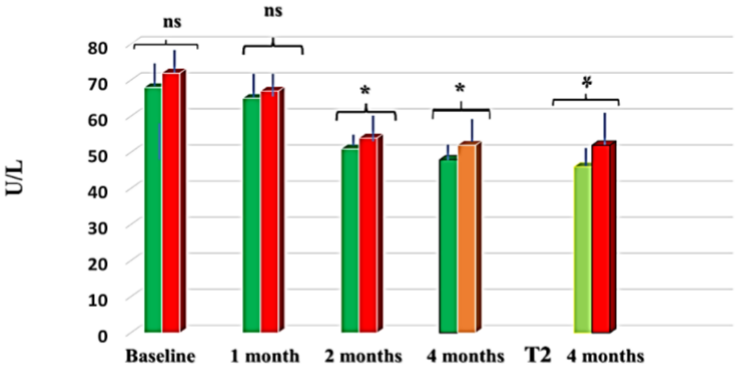


Figure 3b. Plasma level of oxidized LDL: Effect of FPP and multivitamin (52-72 years). Green bars: FPP®, red bars: Multivitamin. Plasma oxidized LDL (absolute values) under the two different nutraceutical treatments. Both treatments yielded a comparative decrease of this parameter in the 52-71-year age cohort (p<0.05 vs baseline). NS: Not statistically significant.

Flow-Mediated Dilation. Baseline FMD did not differ among the groups. There was a time-related significant increase of FMD (p<0.05) in the Multivitamin-treated group. It yielded a substantial change in the observation controls. This effect also appeared in the FPP®-treated group and to a greater degree at 4 months of observation (p<0.05 vs Multivitamin, Figure 5). The crossover analysis confirmed this.

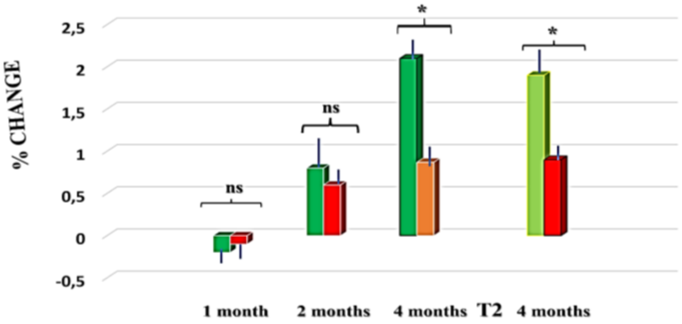


Figure 4. Percentage change FMD: Effect of FPP and multivitamin (55-72 years). Green bars: FPP®, red bars: Multivitamin, ns: not statistically significant.

As for plasma nitric oxide (NO) levels, younger subjects (42-51 y) displayed substantially unchanged values compared to baseline, except for a non-significant trend increase (data not shown; 0.08). When the analysis of this parameter was applied within the 55-72 years age cluster, it appeared that at 4-month observation, FPP treatment yielded a statistically significant increase over the unchanged values observed in the Multivitamin group ($p<0.01$ vs Multivitamin and vs baseline; Figure 5).

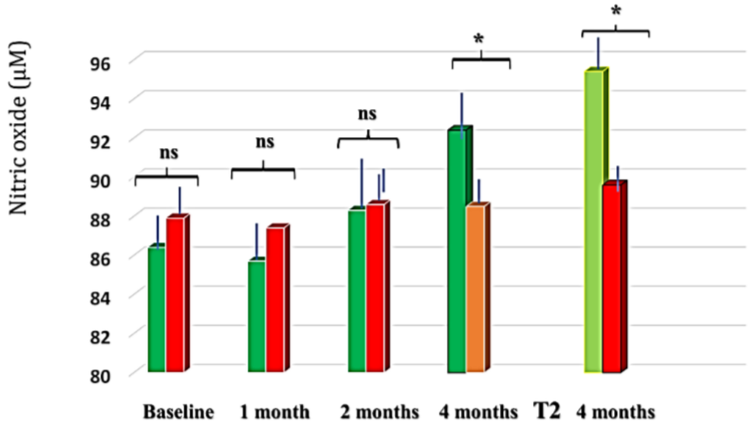


Figure 5. Plasma level of nitric oxide: Effect of FPP and multivitamin (52-72 years). Green bars: FPP®, red bars: Multivitamin, ns: not statistically significant. Data are indicated as mean values ± standard deviation. *Significantly different between groups and from baseline ($p < 0.01$).

DISCUSSION

In recent years, there has been a wealth of scientific reports on the potential benefits of natural compounds for health strategies and as adjuvants to conventional treatments [24-32]. This has prompted learned Western and Asian cooperative groups to work on the regulatory aspects of this field, while also considering commercial pressures, often lacking validated guidelines and credibility [33-36]. In this study, we chose a specific, patented, non-OGM functional food, i.e., Fermented papaya preparation (ImmunAge®, ORI lab, Japan), which is supported by over 20 years of peer-reviewed studies demonstrating its significant redox modulation, inflammation-curbing, and immune-modulation properties [36-38]. We found that both nutraceutical interventions comparably increased intra-erythrocyte ATP concentration. However, FPP® in one set of crossover studies (4 months in T1) yielded a statistically higher value ($p< 0.05$ vs baseline and vs the Multivitamin group). Although the groups had been split by age, gender, and minor health issues, we cannot rule out that the difference may have been due to still-to-be-defined intrinsic RBC aging characteristics and susceptibility to oxidative stress, as we previously showed [39].

On the other hand, at the plasma level, either FPP® or the Multivitamin formula displayed a comparably valid redox modulation capacity as measured by TAC. However, when analyzing the concentration of oxidized LDL, out of the widely scattered data, and focusing on a more specific age group (55-72 years), both treatments effectively decreased this marker, and FPP® yielded the higher percentage decrease from baseline. Of great interest was the finding in this 55-72-year-old group that, unlike Multivitamin, FPP® significantly increased FMD at 4 months of observation. Endogenously, NO is owed to age-related oxidative stress and subtle inflammation, fostering the NO degradation, and hampering its endothelial production, together with an increase in asymmetric dimethylarginine (ADMA), inhibiting NO synthase, and overall poor vascular availability of NO decreases with time [38]. Older subjects have indeed a greater risk for cardiovascular diseases largely because of vascular dysfunction, including reduced endothelial function and aortic stiffening. Beetroot, rich in nitrates, has been assessed frequently in this setting for putative preventive purposes [39-41]. However, the alternative nitrate–nitrite–nitric oxide pathway via higher intake, for instance, of beet root juice, besides having only modest or no antioxidant activity [42], if used for prolonged consumption, may lead to an increase in the formation of potentially gastric carcinogenic [43] compounds, especially in aged people [44]. In other cases, it has failed to provide a significant benefit on vascular function [45]. To encompass the understanding of mechanisms of aging and disease prevention remains a highly challenging task, arduous to fulfill so far, and beyond our trial.

The present study in healthy middle-aged/elderly subjects sheds light on the potential of a biotechnology-controlled fermented functional food, as elsewhere suggested [46], to improve redox balance, cellular ATP content, mitigate ox-LDL, and support vascular endothelial function. As a matter of fact, in a recent article, the profound impact of even small changes in oxLDL and NOx levels has been highlighted over traditional biochemical determinants of vascular aging [47]. This opens new avenues, including herbal, marine compounds, and intestinal ecology modifiers [48-51].

CONCLUSIONS

The present clinical study provides significant data in favour of an interventional strategy against endothelial, redox and bioenergetic dysregulation in aging, and the superiority of (FPP®), a fermented functional food as compared with a synthetic multivitamin.

Abbreviations. NO: nitric oxide, TAC: Total antioxidant capacity, oxLDL: Oxidized follow-upLDL.

Competing interests: The authors declare no conflict of interest in pursuing this research study. All authors jointly cooperated with this work and approved the final version.

Authors' Contributions: FM, JC, OM, RC designed the study; JC, AN, CM, FM did clinical follow-up; RR, MCG, and MAA provided scientific assistance.

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