both supplementations did not stop. This second year of the study, analyzed 98 subjects, (8 of 106 lost at follow up or dropped out for personal reasons or trauma), all clinically stable, healthy community dwelling males and females (m/f: 42/56) aged 58 to 77 years, Due to the extensive duration of the study, participants' engagement in regular daily activities was monitored using a comparable watch-pedometer application, aiming to maintain an average of 6000 steps/day without specific performance targets.

Design of the study: During the second year of the study, the original double-blind protocol was consistently applied, assessing two distinct treatments. The FPP® group (group A) received FPP® 4.5g, 1 sachet twice a day, with an additional placebo capsule (vegan cellulose) before breakfast. Meanwhile, the AA group (group B) was administered a fruit-flavored 4.5g, 1 sachet twice a day, with the morning dose associated with a capsule containing a comprehensive antioxidant mixture (200mg trans-resveratrol, 100mg Centella asiatica extract, 80mg ubiquinol, 50mg epigallo-cathechin-gallate, 20 mg anthocyanidins, 5mg zinc, and 200 IU vitamin E). This formulation was done by the researchers in a compounding pharmacy by putting together ingredients and dosages much popular in the market. Planned blood tests were set as follows: Visit V at 18 months (only clinical assessments) and Visit VI (final clinical and biochemical assessment) at 24 months.

Methods: Morning blood samples were collected from patients after overnight fasting. In addition to routine clinical laboratory tests, performed blindly, the following parameters were tested: Neutrophil-lymphocyte ratio (NLR), an indicator of systemic inflammation [20] was measured by dividing the number of neutrophils by the one of lymphocytes. As in the previous preliminary study, the following tests were also carried out: Ultra sensitivity C-reactive Protein (by a highly sensitive ELISA with a lower detection limit of 0.01 mg/L, serum ADMA level by a commercially available enzyme-linked immunosorbent assay (ELISA) kit for ADMA (DLD Diagnostika GmbH, Hamburg, Germany), yielding a sensitivity 0.01 µmol/L and a the inter-assay coefficients of variation of less than 3% [21], urinary 8-oxo-7,8-dihydro-2'-deoxyguanosine (8OHdG) concentration adjusted for urinary creatinine values [21] by a competitive assay (Oxis Health Products, Inc.). In particular, spot urine samples were collected by subjects in sterile boxes upon awakening (7.00-7.30), before consuming any water or beverages and then taken to the laboratory by 9.00am where they were stored at -70 until the date of assay. Sample aliquots were tested as above for the quantification of 8-OHdG (ng/mL). The urinary creatinine concentration (mg/mL) was quantified by using an ELISA assay kit (Afinion-kit ACR, Italy). The creatinine-adjusted 8-OHdG concentrations (ng/mg) were used for the analysis. To normalize the 8-OHdG concentration distribution, the Box-Cox transformation was used. Univariate associations between subjects' characteristics (age, gender, BMI, fruit, and vegetable consumption) and 8-OHdG concentration levels wase evaluated with a linear mixed-effects regression model for repeated measurements.

Annexin V staining was carried out using anti-annexin V antibody (eBioscience) in annexin V binding buffer kept for 15 min. DAPI staining served to exclude the presence of dead cells and the apoptosis frequency was calculated by using BD LSRFortessa (BD Biosciences, San Jose, CA, USA). Apoptosis of peripheral—Blood Mononuclear Cells (PBMCs, isolated from the whole blood by Ficoll-Paque gradient centrifugation. Profiles of each population were analyzed by Cytomics FC 500 (Beckman Coulter).

Statistical analysis: All tests were performed by SPSS version 22 (IBM Inc., Armonik, NY, USA). The normality of the data was checked and confirmed by the Shapiro-Wilk method. Results are presented with means ± standard

deviations (SD) for continuous variables. We also used the baseline value of FPP® or antioxidant supplementation, as assessed at the start of the study 24 months earlier, to analyze the time-course changes. Differences between the two study groups were calculated by t-test and Chi^2-test while a clear-cut alpha level of 0.05 was set for all analyses.

RESULTS

Forty subjects had normal body mass index (18.5–24.9 kg/m2), and fifty-eight were classified as overweight (≥25 and ≤29.9 kg/m2). As compared to the first year of the study, these data showed a significant increase of overweight (≥25 and ≤29.9 kg/m2) subjects (58 vs 31, *P*<0.05). No significant weight change was noted at the end of the study.

NLR values were comparable between the two treatment groups till the 11th month observation. During this observation period, a notable increasing trend was observed in the AA group, culminating in a statistically significant difference at the 24-month control mark (Figure 1, P<0.05 vs entry level and FPP group).

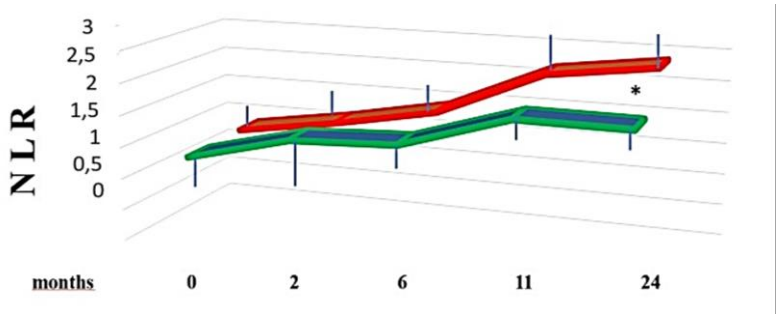

Figure 1. Time-course profile of NLR in both treatments' groups, AA group (red stripe) and FPP-group (green stripe).
* *P*<0.05.

Urinary 8-OHdG values exhibited the previously observed extensive variability between the two groups at baseline (data presented in the previous publication). However, when analyzing these values in subjects aged over 70 or with a BMI exceeding 27, urinary 8-OHdG values were significantly elevated compared to the overall entry level (P<0.05). Both supplementations' regimes equally improved this variable (Fig 2, *P*<0.05) with FPP® effect started being significant already at 6months till the end of the study (24 weeks).

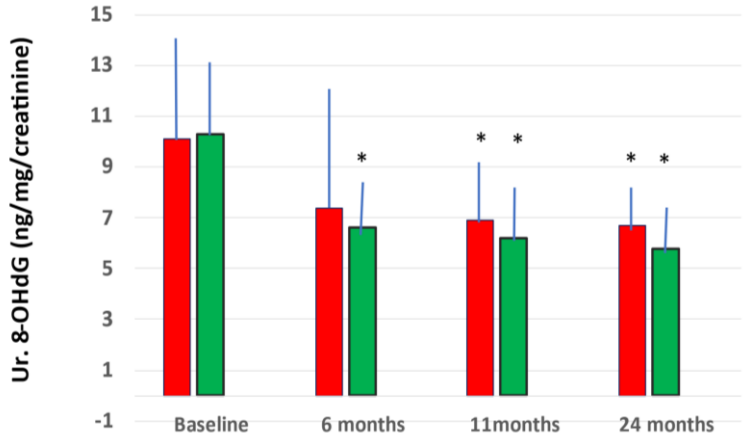

Figure 2. Time-course effect of AA supplemented group (red bars) and FPP-supplemented group (green bars) on the profile of urinary 8OHdG level in in the cohort of participants older than 70 years or with BMI >27. Both supplementations enabled a significant and comparable decrease of this parameter as compared to entry level (*P*<0.05).

In contrast, ADMA values remained unaffected by AA supplementation (Fig. 3), while FPP administration exhibited a notable and significant decrease, observed from the 6-month checkpoint onward (P<0.05 compared to baseline and AA supplementation).

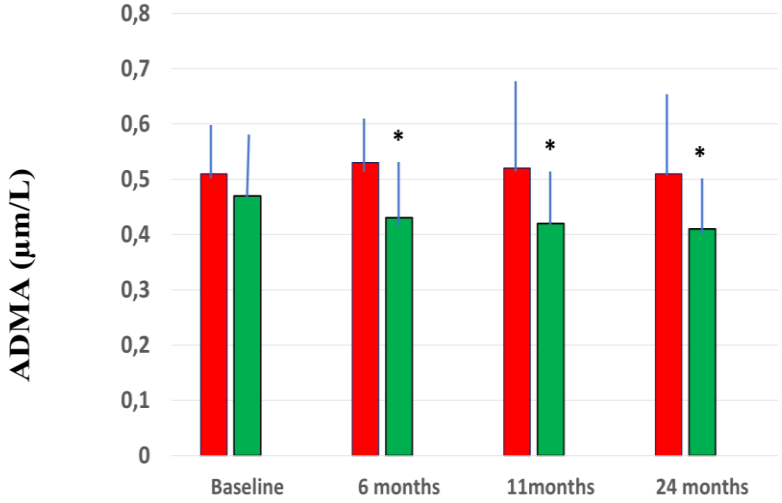

Figure 3. Time-course changes of plasma ADMA level in AA supplemented group (red bars) and in FPP-treated group (green bars). Differently from AA treatment, FPP® supplementation yielded a significant decrement till to 24 months control (*P<0.05 vs baseline and AA group).

At the study's onset, there was no notable difference in the frequency of apoptotic cells in PBMCs between the two treatment groups (Fig. 4). Following the 6th month of the trial, the AA group exhibited a gradual and significant increase (P<0.05 compared to baseline). In contrast, the FPP®-administered group showed only a slight, non-significant trend increase while maintaining an overall stable lower percentage (P<0.05 compared to AA group values observed at 6, 11, and 24 months).

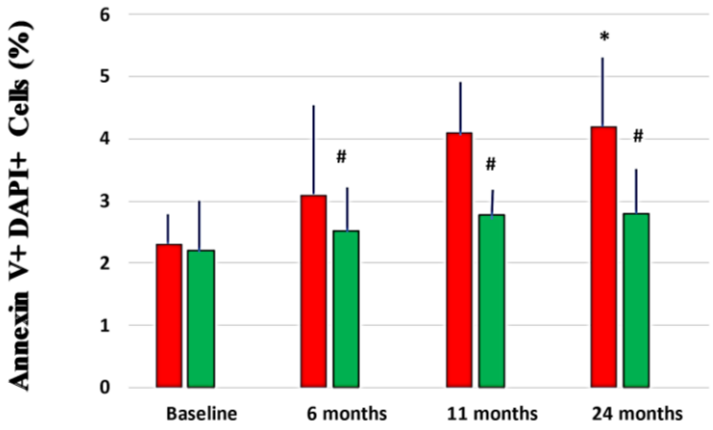

Figure 4. Frequency of apoptotic cells (Annexin V+ DAPI+) at baseline, 6, 11 and 24 months. While this parameter remained fairly stable throughout the 24 month follow up in the FPP® group (green bars) (#P<0.05 vs AA group),), In the AA group (red bars), a notably steep increase was observed at 6 months, and more prominently at 11 and 24 months, reaching statistical significance (P< 0.01 compared to baseline).

Table 1 shows the level of statistical significance when correlating the values of NLR and Apoptosis of PBMCs throughout the study period. It appeared that, at 11 months and 24 months, the two parameters were highly correlated, and this was more pronounced in those participants older than 70 years or with BMI >27.

Table 1. Correlation between NLR and Apoptosis of PBMCs in FPP-supplemented group

Elements of correlation	**2 weeks**	**6 weeks**	**11 weeks**	**24 weeks**
NLR Apoptosis (PBMCs)	r = 0.545 ns	r = 0.524 ns	r = 0.759* **P*<0.05 vs baseline	r= 0.772* **P*< 0.05 vs baseline
participants older than 70 years or with BMI >27				
NLR Apoptosis (PBMCs)	r = 0.443 ns	r = 0.546 ns	r = 0.791* **P*<0.005 vs baseline	r = 0.813** ***P*<0.005 vs baseline

No correlation appeared between NLR and hCRP, Ur-8OHdG or ADMA at any of the time-check, irrespective of the gender (data not shown). No correlation appeared when analyzing AA group separately, irrespective of age and BMI, ns: not statistically significant.

DISCUSSION

The initial broad range of data observed during the urinary 8-OHdG level assessments in the first year of the study did not allow for definitive conclusions regarding the impact of nutraceutical interventions. This observation persisted until the conclusion of the second-year investigation (data not presented). This finding is not surprising, when considering the disappointing or modest results reported in the past by using vitamin C or E [24-25] and where also the role of diet [26] was not specifically ruled out. For instance, dietary regimens prescribed for chronic benign diseases have indirectly shown to act as cancer protectors [27]. Moreover, such studies, to optimize the homogeneity of the diet, would need a detailed food bioactive components and probiotic content analysis [28-31]. However, the extended duration of the study confirmed the stability of the results observed during the initial year, persisting until the 24-month observation. . This is significant when considering the increased number of recruited overweight patients (58 vs 31, *P*<0.05) and aged subjects. This data is in agreement with the observation of drastic improvement of this plasma and urinary parameter after weight loss surgery [32]. NLR can be regarded as a correlated marker of oxi-inflammatory imbalance, associated with cardiovascular disease risk, and serves as a prognostic factor for atherosclerosis, aging, overall mortality, cancer progression, and rheumatoid arthritis [33-39]. This has also been reported in advanced chronic gastritis by Helicobacter Pylori [40]. Nevertheless, even though none of our subjects reported gastric symptoms, considering the susceptibility of the aged population group to oxidative damage [41], we cannot exclude the potential presence of gastric atrophy with various immune-inflammatory mucosal rearrangements [42]. The anticipated positive effects of FPP [43] at this specific

level are evident, as demonstrated in a clinical study [44]. Interestingly, NLR and ADMA, although not yielding a statistical correlation between each other, showed a similar higher level and, unlike the AA group, both parameters significantly responded to FPP® at 11 and 24 monthss. Exercising due caution due to the severity of the disease, a recent study conducted on hospitalized SARS-CoV-2 patients revealed an association between mortality and concurrent abnormalities in NLR and ADMA [45]. This supports the prognostic value of ADMA assessments in these patients, both during hospitalization and throughout the post-COVID syndrome period, which is still not fully understood [46-50]. Although none of our patients had diabetes, we did not conduct HOMA testing. In this expanded group of overweight individuals, HOMA testing might have revealed insulin resistance in some cases. Existing literature clearly highlights that NLR abnormality is associated with this condition [51] and is responsive to antioxidant treatment [52]. Although our study did not address cerebrovascular pathophysiology, a recent review from Framingham Heart Study has reported that subjects with higher NLR are at a greater risk of later dementia during a 5.9-year follow-up period [53]. This area is understandably of extremely complex metabolic interrelations, either environmentally (exotoxins) [54, 55] or internally (endotoxins) [56].

In this nutritional interventional setting, Belpomme's group [57], by using FPP®, has demonstrated a statistically significant clinical and redox benefit together with an increase in intracerebral tissue pulse metric index in the temporal lobes through ultrasonic brain tomosphygmography and whose long-term relevance warrants follow up studies. Amid the accumulating evidence of effective functional foods influencing brain physiology [58-64], this signifies a step beyond the raised caution associated with intrinsic methodological variables in in vitro analysis [65]. In the quest for a rational science-validated functional food [66] and more controlled selection of bioactive compounds [67], FPP represents a substantial demonstration of pharma-grade, non-GMO technological advancement over traditional carica papaya use [68]. The ongoing pursuit of healthy living inevitably involves impacting a fundamental oxi-inflammatory phenotype to varying degrees [69-71]. In this context, NLR monitoring [72] may be a marker worth great attention [73-75] and preventive interventional potential in middle-aged/elderly communities health care [76-77]. The novelty of the present study resides in a long-term monitoring of key age-related parameters while using a functional food treatment.

CONCLUSION

This groundbreaking study represents the first two-year monitoring of the effects of antioxidants and a novel functional food (FPP) on key redox parameters, PBMCs apoptosis, and the NLR, with a particular emphasis on the long-term impact. While the antioxidants mixture exerted a significant effect on redox parameters, on top of this, FPP was shown to bring about age/health- and longevity-associated immune system markers. This finding may help substantiate health maintenance strategies.

Abbreviations: NLR: neutrophil-lymphocyte ratio, i.e. the number of neutrophils divided by the number of lymphocytes; ADMA: Asymmetric dimethylarginine; PBMCs: Perypheral Blood Mononuclear Cells; FPP®: Fermented Papaya Preparation; BMI: Body Mass Index; 8OHdG: 8-oxo-7,8-dihydro-2'-deoxyguanosine

Contribution: OM, SU discussed the research plan, LA and RS followed the clinical aspects FH and AC discussed and evaluated nutritional aspects, AA and US discussed and evaluated the biochemistry.

Conflict of interest: Authors declare no personal or institutional conflict of interest.

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