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Safety and Genoprotective Effects of an 8-Herb Tea–ESSIAC Versus Mate Cocido, An *Ilex paraguariensis* Infusion

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Abstract

ESSIAC tea is a traditional multi-herb infusion or decoction widely used by cancer patients as a complementary therapy. Originally employed in traditional Ojibwa medicine, it was later reformulated by a Canadian nurse. The classic ESSIAC infusion contains four main botanicals: burdock root (*Arctium lappa*), Turkish rhubarb root (*Rheum palmatum*), sheep sorrel (*Rumex acetosella*), and slippery elm bark (*Ulmus rubra*). Commercial variations (e.g., FlorEssence® and Genuine ESSIAC™) expand this list to include blessed thistle (*Cnicus benedictus*), kelp (edible Laminaria seaweeds), red clover (*Trifolium pratense*), and watercress (*Nasturtium officinale*). Although they are commercially available, human safety data are limited. We conducted an exploratory analysis registered at the Central Ethics Entre Ríos Provincial Committee Board, of the Provincial Minister, and Ethical Committee of CCT-CONICET Santa Fe

(Committee Ref #: CES-00641) to evaluate the safety and DNA-protective effects by comet assay of an 8-herb tea in healthy adults and compared it to a traditional infusion of mate cocido, of *Ilex paraguariensis*. Participants consumed 200 mL/day for 6 weeks; pre- and post-assessments included blood chemistry and an alkaline comet assay. Twenty-four participants completed the study (12 per arm). Adherence was high, and no serious adverse events occurred. Laboratory indices remained within reference ranges in both groups, as well as for DNA damage, as the percent DNA comet tail declined from week 0 or baseline in both arms. Overall, daily ESSIAC tea was well tolerated and did not adversely affect laboratory indices. The observed genoprotective trend in both groups is consistent with the antioxidant phytochemicals present in the herbal infusion. These results support the safety of ESSIAC tea and justify larger trials to assess its complementary roles.

Keywords
Brewed tea; mate cocido; comet assay; DNA damage; antioxidants; daily ingestion

1. Introduction

ESSIAC tea is a traditional herbal blend widely used by cancer patients as a complementary therapy [1-3]. Originally employed in traditional Ojibwa medicine, it was later reformulated by Canadian nurse René Caisse in the 1920s. The classic ESSIAC decoction contains four main botanicals: burdock root (*Arctium lappa*), Turkish rhubarb root (*Rheum palmatum*), sheep sorrel (*Rumex acetosella*), and slippery elm bark (*Ulmus rubra*). Commercial variations (e.g., FlorEssence®) expand this list to include blessed thistle (*Cnicus benedictus*), kelp (edible Laminaria seaweeds), red clover (*Trifolium pratense*), and watercress (*Nasturtium officinale*) [3, 4]. In vitro and preclinical studies have demonstrated ESSIAC's capacity to scavenge free radicals, reduce DNA strand breaks, and modulate enzyme systems such as CYP3A4 [5]. Leonard et al. reported potent antioxidant activity of ESSIAC in neutralizing superoxide and hydroxyl radicals and preventing hydroxyl-induced DNA strand breaks [5].

Martinez Marignac et al. observed reduced X-ray-induced genotoxicity in mice consuming ESSIAC [4]. However, systematic reviews and observational data have raised concerns about inconsistent formulation and lack of robust human clinical trials [1-6].

A North American, retrospective phase 1 trial by Richardson et al. [3], designed as a pattern-of-use survey of 5051 Flor-Essence™ consumers (response rate 6.4%), demonstrates that most were long-term users (mean 15.8 ± 17.4 months) treating medical conditions, particularly cancer [3]. Among 1560 cancer patients, 88.6% adhered to the recommended ≤4 oz/day dose, while 11.4% reported exceeding it [3]. This study reported that adverse events were uncommon (6.6%), the most frequent being diarrhea (1.9%), constipation (1.2%), nausea (1.1%), and fatigue (0.9%) [3].

Although 64.5% discussed tonic use with physicians and 50.6% perceived symptom improvement, the remarkably low incidence of adverse events observed in retrospective analyses underscores the need for rigorous prospective, controlled trials to definitively establish the safety and tolerability profile of ESSIAC. Moreover, extensive phytochemical investigations of each botanical component within the ESSIAC formulation have identified a spectrum of bioactive compounds such as flavonoids,

phenolic acids, polysaccharides, and anthraquinones, which exert antioxidant, anti-inflammatory, and glycomodulatory effects in preclinical models. *Arctium lappa* (burdock) is rich in polyphenolic antioxidants (e.g., caffeoylquinic acids) and flavonoids; its extracts have demonstrated anti-oxidative and lipid-lowering actions in animal and in vitro models [7-10]. *Rheum palmatum* (Turkish rhubarb) provides anthraquinones such as emodin, aloe-emodin, and rhein, which exhibit anti-proliferative and pro-apoptotic effects on cancer cells through multiple signaling pathways [11, 12]. The component *Rumex acetosella* (sheep sorrel) similarly contains antioxidant anthraquinones, though high doses can cause mild laxation and electrolyte loss [13]. *Ulmus rubra* (slippery elm) contributes mucilaginous polysaccharides thought to soothe mucosal tissues, and has a history of use for gastrointestinal inflammation, but scientific data on its antioxidant effects are limited [14, 15]. Other ESSIAC ingredients like *Trifolium pratense* (red clover) and *Cnicus benedictus* (blessed thistle) contain isoflavones and flavonoids that modulate metabolism and inflammation [16-18].

The other two compounds, kelp and watercress, affect glycemic and lipid metabolism [19-22]. Overall, ESSIAC is a concentrated source of polyphenols and related compounds that, in principle, could scavenge reactive oxygen species (ROS) and ameliorate oxidative stress [4, 5].

Oxidative stress and resultant DNA damage are hallmarks of cancer and aging-related pathologies [4]. Many dietary phytochemicals exert chemopreventive effects by bolstering antioxidant defenses or enhancing DNA repair; however, they may present interactions with different treatments [5, 23, 24].

The control selected was mate cocido or yerba-mate (*Ilex paraguariensis* A.St.-Hil.), it was selected as it has a similar taste to Genuine ESSIAC™ tea blend, and it is popular and part of the breakfast in Argentina. Yerba mate is a native plant from South America, highly consumed in this region in different traditional presentations, such as yerba mate, mate tea, mate cocido, and tereré, obtained from the yerba-mate leaves and consumed as an herbal infusion [25, 26]. Yerba mate is a rich source of bioactive phenolic compounds, mainly caffeoylquinic acids. The richness of different mono- and dicaffeoylquinic acids is a peculiarity of yerba mate-derived products. However, in contrast to other plant-based beverages rich in polyphenols like tea or coffee, the research and the industry have yet to explore the potential interest of yerba mate products to promote human health despite its daily consumption [25, 26].

Given its widespread use among oncology patients and its potential DNA-protective effects, rigorous clinical assessment of ESSIAC tea's safety and efficacy by a formal, prospective clinical evaluation is justified [3-5]. We therefore conducted a fixed-dose, exploratory Phase I study designed to assess short-term tolerability, safety, and preliminary biological signals rather than dose-response relationships or efficacy throughout the 6-week intervention. Because the study objective was to evaluate safety under closely monitored conditions, dose escalation was not part of the design. We conducted a prospective randomized exploratory trial to assess whether daily ingestion of ESSIAC tea is safe and to explore its effects on blood biochemistry and genomic integrity (via the alkaline comet assay) in healthy volunteers. The use of a single standardized dose allowed us to focus on adherence, adverse events, and within-range biochemical and comet-assay outcomes. Therefore, the findings should be interpreted as more hypothesis-generating, safety-exploration, rather than as confirmatory evidence of efficacy. Therefore, we hypothesized that an eight-herb ESSIAC decoction would be well tolerated, reduce leukocyte DNA strand breaks compared to our control choice, and have beneficial effects in the short term.

2. Materials and Methods

2.1 Study Design and Participants

This single-site Phase I study was conducted from October to November 2023 at IBioGeM in Entre Ríos, Argentina. The design was prospective, randomized, double-blind, controlled, and approved by the Ethical Committee of CCT-CONICET Santa Fe (Reference number: CES-00641) and the Central Ethics Entre Ríos Provincial Committee Board. Participants were randomly assigned to receive either ESSIAC tea decoction or a control infusion (mate cocido) over six weeks.

Healthy adult volunteers (age ≥18) employed at health care institutions with radiation-image services were recruited. Participants were recruited from healthcare institutions, including facilities with radiology and other X-ray services, as this population represents a relevant context for exploratory biomonitoring and genomic safety evaluation. Key inclusion criteria were hemoglobin ≥10 g/dL, platelets ≥75,000/μL, and neutrophils ≥1,500/μL. Exclusion criteria included known herb allergies, active infections (HIV, hepatitis), significant cardiovascular disease, recent surgery, psychiatric conditions, pregnancy/lactation, or recent participation in similar studies within 30 days.

Volunteers who met the criteria answered an initial structured interview and provided informed consent were randomly assigned (1:1) to either the ESSIAC or control group using a computer-generated list. Investigators and subjects were blinded to allocation. All subjects received 2 L/week of their assigned infusion (200 mL daily) to consume in the morning on an empty stomach.

2.2 Study Interventions: Decoction and Infusions

Regarding the comparator, yerba mate is not an inert placebo but an active herbal infusion with its own polyphenol content and biological activity. Therefore, the use in this study was explicitly for blinding and cultural acceptability; this choice may limit attribution of any between-group differences exclusively to ESSIAC, rather than to radioprotection or other effects.

The Genuine ESSIAC™ decoction was prepared each week by boiling 28 g of a standardized eight-herb blend (Genuine ESSIAC™, Massachusetts, USA, formula) in 1.2 L of mineral water for 10 minutes, then steeping for 12 hours (as recommended by the manufacturer). The resulting infusion was refrigerated and dispensed in daily 200 mL doses. The control was “brewed mate” (mate cocido) prepared identically from 28 g of commercial yerba mate leaves and administered in 200 mL daily fasting doses. Mate cocido was chosen for its color and taste, as a non-inert placebo and a well-tolerated control. Both infusions were bottled and labeled by a laboratory technician to preserve blinding.

Participants were instructed to continue their usual diet and lifestyle as per the initial interview, but to avoid other herbal supplements or high-polyphenol interventions during the study, such as black tea and yerba mate infusions. Compliance was assessed by returned volume measurements; all subjects consumed >90% of doses and completed a final structured interview on lifestyle and basic health parameters.

2.3 Outcome Assessments

Baseline (week 0) and end-of-study (week 6) assessments included venous blood collection after more than 2 hours fast. Laboratory tests, including complete blood count, liver enzymes (Alanine

Aminotransferase ALT, Aspartate Aminotransferase AST, Alkaline Phosphatase ALP), liver function (Total bilirubin T Bil and direct bilirubin D Bil), renal function (Serum Creatinine-Cr), fasting glucose, and lipid panel (total cholesterol, HDL, triglycerides) were performed by an independent clinical laboratory at a Clinical Center.

Genomic damage was assessed using the alkaline comet assay (ACA) according to previously standardized and published methodologies from Martinez Marignac et al, 2020 [4] and Cardoso et al., 2022 [27]. For the comet assay (ACA), fresh blood samples obtained before and after the intervention period were processed immediately for single-cell gel electrophoresis. Cells were embedded in agarose on slides, lysed, subjected to alkaline electrophoresis, and stained. For each individual sample, 50 nucleoids were evaluated using digital image-based scoring, and the median % tail DNA per participant was used for statistical analysis, as this metric reduces the impact of outlier cells and supports more stable interpretation. To improve methodological rigor, all slides were coded and analyzed under blinded conditions, and all samples were processed and scored within the same analytical batch, thereby minimizing observer bias and reducing inter-assay variability. This approach is widely used in comet assay applications for human biomonitoring and exploratory genomic safety studies [27]. The initial % of damage at week 0 was set as a baseline for genotoxicity determination.

Subjects were seen weekly for safety monitoring. Adverse events (AEs) were recorded and graded according to Common Terminology Criteria for Adverse Events (CTCAE version 3.0). Vital signs and any symptoms were noted. No subjects were lost to follow-up due to safety concerns.

2.4 Statistical Analysis

Given the exploratory Phase I design, the analysis was primarily descriptive. Continuous variables were summarized as medians and ranges (or means ± SD) within each group; categorical variables as counts and percentages. Changes from baseline to week 6 were described by group. Outcomes (laboratory values, % tail DNA) were compared qualitatively between baseline/week 0 and week 6 within each group, and trends across groups were noted. Hypothesis testing was performed as per an exploratory phase 1 trial according to FDA guidance [28]. Group comparisons were performed by paired T-test, Wilcoxon signed-rank tests, and Mann–Whitney U tests with a two-sided $\alpha = 0.05$ threshold as applicable. All data analysis was conducted using the online platform https://www.statskingdom.com/paired-t-test-calculator.html. Social Science Statistics platform socscistatistics.com and the test were validated by JASP (Version 0.95.4), curated by the University of Amsterdam [29], a free-access software.

2.5 Ethics Statement

The study was conducted in accordance with the principles of the Declaration of Helsinki. It was approved by the Central Ethics Entre Rios Provincial Committee Board and registered by the Ethics and Experimental Safety Committee of the Science and Technology Center (CCT) Santa Fe province - (CEYSTE), CCT SANTA FE, reporting to the National Council for Scientific and Technical Research of Argentina (CONICET), register number, Nro. 0641/2022.

3. Results

3.1 Participants

Thirty-seven participants were contacted, of whom 27 met eligibility criteria, were enrolled, and adhered to start the study. Thirteen were assigned to ESSIAC tea, and 14 to control. Table 1 shows the demographic profile of the recruited volunteers. Twenty-four participants (18 female, 6 male; mean age 44.1 ± 7.6 years) adhered to the protocol and completed the 6-week regimen and an end interview.

Table 1 Baseline characteristics and adverse events (AEs) by study group, ESSIAC and Control (n = 12 per arm). The results are median and range in years for age, n = size, and % = percentage for gender and AEs.

Characteristic/Event	ESSIAC (n = 13)	Control (n = 14)
Age, years (median, range)	49 (28-62)	51 (36-65)
Female sex, n (%)	9 (75%)	9 (75%)
Adverse events (AEs)		
Nausea	1 (8%)	2 (14%)
Vomiting	0	2 (14%)
Diarrhea	0	1 (7%)
Any GI symptom*	1 (8%)	2 (14%)
Total adherence	12 (92%)	12 (86%)

*GI symptom:gastrointestinal symptom, Grade 2 gastrointestinal symptoms were observed, leading to early discontinuation; all ARs (adverse responses) were transient and resolved without treatment.

3.2 Tolerability and Adverse Events

Overall tolerability was excellent. Three participants (12%) experienced only mild gastrointestinal AEs during the study (Table 1). In the ESSIAC group, one subject had grade 2 nausea on two non-consecutive days. In the control group, two subjects had combined nausea, vomiting, and/or diarrhea (each grade 2). All GI events were transient; no subject required medical intervention or hospitalization, and they were withdrawn from the trial. There were no reports of headache, insomnia, or other symptoms. No severe (grade 3+) or unexpected adverse events occurred in either arm. The laboratory studies revealed no clinically significant abnormalities attributable to the interventions.

3.3 Biochemical Outcomes

Laboratory values remained within reference and normal ranges for all subjects at all timepoints. Neither ESSIAC nor control induced clinically meaningful changes in blood counts, renal function, or glycemic indices. Lipid profiles showed no change in triglycerides and modest but consistent improvements in both arms by week 6. Median total cholesterol fell by 10% (from 219 to 190 mg/dL in the control group). However, HDL cholesterol increased slightly in both groups and was significant in the ESSIAC cohort (Table 2). The paired T-test analysis indicates a robust, within-subject increase

in HDL after the intervention: mean difference +3.25 mg/dL (SD 2.05), paired t-test (11) = 5.49, p = 0.00019; Wilcoxon p = 0.00049; permutation p = 0.0005; paired bootstrap 95% CI 2.25-4.42 mg/dL; Cohen's dz = 1.58. Normality testing of the paired differences did not reject normality (Shapiro–Wilk p = 0.103), and leave-one-out checks show the effect remains highly significant when any single observation is excluded, so the finding is statistically robust and not driven by a single influential value. Liver enzymes (AST) significantly increased for ESSIAC, while in the control group remained stable, the increase in AST of +1.17 units (paired t-test p = 0.032; Wilcoxon p = 0.042; paired bootstrap 95% CI 0.25-2.00; Cohen's dz = 0.71) indicates a small, reproducible biochemical shift that merits careful but circumspect interpretation as can not confirm normality (Table 2). Furthermore, three other liver indicators, ALP, D-Bil, and T-Bil, were significantly decreased in the ESSIAC group. ALP declined after the intervention by a mean of 6.75 U/L (SD 5.64). Paired t test: t(11) = -4.14, p = 0.0016. Shapiro–Wilk W = 0.957 (p = 0.743). Wilcoxon signed-rank p = 0.0048; permutation p = 0.0032; paired bootstrap 95% CI -9.83 to -3.75. Leave-one-out sensitivity checks retained significance. Although the results, all values remained within normal reference ranges. In addition, both conjugated bilirubin (D-BIL) and total bilirubin (T-BIL) declined (D-BIL mean -0.14 mg/dL, Wilcoxon p = 0.00049, permutation p = 0.0005, bootstrap CI -0.18 to -0.11; T-BIL mean -0.44 mg/dL, paired t p = 0.024, permutation p = 0.0166, bootstrap CI -0.77 to -0.13).

Table 2 Key clinical laboratory analysis results and DNA damage outcomes at baseline/week 0 and week 6. Values are median (range) for each group (n = 12).

Clinical Parameter	ESSIAC Week 0	ESSIAC Week 6	Control Week 0	Control Week 6
ALT (U/L*)	12 (9-13)	11 (9-15)	13 (9-20)	12.5 (9-18)
AST (U/L)	6 (5-10)	8 (6-10)*	8 (5-18)	8 (6-10)
ALP (U/L)	103 (82-120)	96 (82-107)*	102 (87-171)	94.5 (88-106)
D-Bil (mg/dL*)	0.33 (0.3-0.6)	0.20 (0.1-0.3)*	0.30 (0.2-1.3)	0.2 (0.1-0.6)
T-Bil (mg/dL)	5.7 (4.4-7.6)	5.20 (4.9-7.2)*	5.7 (4.6-8)	5 (4.3-6.6)
Cr (mg/dL)	0.93 (0.8-1.1)	0.94 (0.9-1.1)	0.94 (0.73-1.09)	0.92 (0.87-1.04)
Total cholesterol (mg/dL)	243.5 (151-282)	235 (135-270)	219 (160-280)	190 (160-255)
HDL cholesterol (mg/dL)	45.5 (39-51)	48.5 (44-54)*	46 (40-69)	48.5 (42-51)
% DNA in comet tail	18 (6-57)	3 (0-15)[#]	8 (1-22)	2 (1-32)[#]

*U/L and mg/dL conventional units of clinical reports for Alanine Aminotransferase ALT, aspartate aminotransferase AST, Alkaline Phosphatase ALP, Total bilirubin T Bil, direct bilirubin D Bil, Serum Creatinine-Cr, total cholesterol, HDL.

[#]Statistically significant differences were observed by paired T-test analysis.

3.4 DNA Damage (ACA)

At week 0, median leukocyte DNA damage (% DNA in comet tail) was low to mid-normal in both groups (ESSIAC: 18%; Control: 8%). At week 6, DNA fragmentation declined and was statistically significant in both arms (paired T-test p = 0.03, Table 2). The ESSIAC group showed median tail DNA of 10% to 7% at weeks 0 and 6, respectively; in the control, the median tail DNA was 9% to 8%. While between-group comparisons were not statistically significant, the ESSIAC arm showed a larger absolute reduction.

In an exploratory post-hoc analysis, we stratified subjects by week 0 damage into two groups: those with damage below 10% and those with damage above 10%. Among participants with elevated week 0 tail DNA (>10%), those receiving ESSIAC exhibited a significant reduction in % tail DNA by week 6 (e.g., median 14.8% → 7.1%). In contrast, fewer subjects in the control arm had a high baseline of 10% damage at week 0, and no significant change was demonstrated in this cohort. Overall, the decrement in DNA breaks was evident in both groups, but the magnitude was greatest in the ESSIAC-treated subset. No subject had an increase in DNA damage with either infusion or decoction.

4. Discussion

A tea of 4 to 8 herbs, marketed as ESSIAC and Flor-essence, is widely used by North American cancer patients during chemotherapy and radiation therapy. Although ESSIAC is currently unavailable for sale in Canada, the Canadian government allows its sale to patients on compassionate grounds [2, 3, 30, 31]. By 2009, ESSIAC was graded C under the Natural Standard Grades in Canada, which reflects the level of scientific evidence supporting the efficacy of a given therapy for a specific indication, in this case, cancer [2].

Regarding ESSIAC safety, Richardson et al. [3] have reported a 6.6% overall adverse event rate among 5051 Flor-essence users, with the most common symptoms being diarrhea (1.9%), constipation (1.2%), nausea (1.1%), and fatigue (0.9%). These low rates of primarily mild gastrointestinal effects underscore the favorable tolerability profile and support further prospective, placebo-controlled evaluation of ESSIAC's safety.

There was a lack of prospective, randomized, controlled trials evaluating its safety. Our first-in-human prospective study demonstrates that daily consumption of an 8-herb ESSIAC tea is safe and well-tolerated in healthy adults. Over six weeks, no serious adverse events or laboratory toxicities were observed. Mild gastrointestinal complaints (nausea, vomiting, diarrhea) occurred in only 12% of participants and were self-limited. Moreover, extensive phytochemical investigations of each botanical component in the ESSIAC formulation have identified a diverse array of bioactive compounds as flavonoids, phenolic acids, polysaccharides, and anthraquinones, which exert antioxidant, anti-inflammatory, and glycomodulatory effects in preclinical models [31-36]. These mechanistic insights not only rationalize the composite therapeutic potential of the ESSIAC blend but also provide a scientific foundation for interpreting our clinical outcomes and optimizing dosage strategies in future trials [37].

Our tolerability results align with expectations for polyphenol-rich herbal beverages: transient GI discomfort (nausea, bloating) is commonly reported with green tea extracts and similar infusions [24-26, 31-36]. Importantly, no hepatotoxicity or hematologic adverse events emerged, and fasting glucose remained stable. The ACA results mirrored preclinical animal data; for example, Martinez Marignac et al. reported that 7-week ESSIAC tea ingestion in mice did not cause weight loss, glucose changes, or changes in blood counts [4]. Our data confirm that clinically significant organ toxicity is unlikely at usual consumption levels. Our biochemical analyses showed that liver enzymes (AST) increased significantly with ESSIAC. Mechanistically, such a modest AST rise can reflect transient hepatocyte adaptive responses to bioactive botanical constituents, extra-hepatic release (e.g., minor skeletal muscle turnover or recent exertion), or short-lived alterations in mitochondrial/redox signaling, rather than a toxic effect [31, 32].

All individual values in both cohorts remained within conventional clinical reference ranges, and there were no concurrent clinical signs of hepatic dysfunction. In fact, we observed modest improvements in lipid profiles and stable (or slightly reduced) liver enzyme levels in both the ESSIAC and mate cocido arms. Biochemically, a reproducible rise of this magnitude in HDL is consistent with favorable modulation of reverse cholesterol transport and HDL metabolism rather than an adverse change. Dietary polyphenols and multi-herb infusions have been shown to improve HDL or HDL function by up-regulating apolipoprotein A-I expression, enhancing LCAT activity, reducing CETP-mediated HDL remodeling, and lowering systemic inflammation that otherwise remodels and depletes HDL particles [31-34]. In practical terms, because all individual HDL values remained within conventional clinical reference ranges, the observed mean increase should be interpreted as a beneficial metabolic shift (improved HDL quantity and plausibly function) rather than a safety concern. To strengthen mechanistic inference and clinical relevance, follow-up measures are recommended in future works: quantify ApoA-1, assess cholesterol-efflux capacity (functional HDL assay), and measure CETP/LCAT activity and inflammatory markers; also replicate in a larger, prespecified trial that includes adjustment for multiplicity and stratification by baseline lipid status [30-36].

In our present study, the control employed, mate cocido, was selected because it has a similar taste to ESSIAC tea and is popular and part of breakfast in Argentina. However, in contrast to other plant-based beverages rich in polyphenols like tea or coffee, the research and the industry have yet to explore the potential of brewed yerba mate products to promote human health despite their widespread daily consumption in South America and Argentina [26].

Overall, the data may support a new hypothesis that the herbal infusion exerts favorable lipid-modifying effects consistent with prior trials of tea and polyherbal beverages [30-36]. Crucially, neither infusion impaired liver or renal function during the 6-week trial; this disagrees with some reports indicating that moderate tea polyphenol intake seldom causes organ toxicity [10, 17, 18, 25, 30-36].

In summary, no hepatotoxicity, nephrotoxicity, or hematologic toxicity was observed with daily ESSIAC or yerba mate consumption. These findings align with clinical analyses showing that regular consumption of tea polyphenols typically has neutral or modest beneficial effects on liver enzymes [9, 10, 18-20, 33-35].

Our genotoxicity data, through ACA, suggest a protective trend for both infusions, rather than only safety; these results warrant a new hypothesis-testing trial. The inclusion of healthcare personnel employed in institutions with radiology or other X-ray-associated services was intentional, as such environments may involve chronic low-dose occupational exposure to ionizing radiation. Previous human biomonitoring studies, including comet assay-based evaluations such as Martínez et al. [38] and Zabarmawi et al. [39], have reported increased DNA damage in occupationally exposed healthcare workers. Accordingly, this cohort was considered relevant for an exploratory genomic safety assessment, indicating that occupational exposure may have contributed to baseline/week 0 variability and to DNA damage more severe than that of the normal population in comet assay outcomes.

Notably, subjects with higher initial DNA damage responded strongly to Essiac, and both groups showed reductions in DNA damage, likely because the control was not inert. Moreover, randomization allocated more “high-damage” individuals to the ESSIAC arm (though medians were similar), creating a potential regression-to-the-mean effect, where inter-individual comparisons

were needed. Furthermore, it could mean the between-group difference underestimates any true effect of ESSIAC. A neutral placebo (e.g., water) and/or stratified randomization in future trials might better isolate ESSIAC's unique impact. The reduced DNA strand breaks in the ESSIAC group by week 6 were consistent with preclinical antioxidant effects [4, 5]. Leonard et al. demonstrated that ESSIAC scavenges superoxide and hydroxyl radicals and prevents free-radical–induced DNA damage in cultured cells [5]. Likewise, Martinez Marignac et al. reported that mice given ESSIAC had significantly lower X-ray–induced DNA lesions compared to controls [4].

However, the DNA protection results must be interpreted cautiously, as mentioned above. The brewed yerba mate is rich in antioxidants and has been shown to protect DNA in vitro as well [26]. Biologically, the observed DNA trends are plausible. Dietary antioxidants have been linked to upregulation of DNA repair pathways and prevention of mutagenesis in preclinical models [4, 40].

Our study has limitations: The small sample size and exploratory design preclude definitive efficacy conclusions; the use of yerba mate as an "active" control, while preserving blinding, introduced confounding antioxidant effects biases; Another limitation is that, although participants completed a structured interview, where they were asked to maintain their usual lifestyle, and to avoid additional herbal interventions, dietary, lifestyle-related and occupational factors affecting oxidative stress were not fully controlled. As observed in similar exploratory human studies, such factors may influence oxidative stress-related endpoints and contribute to biological variability. Nonetheless, this proof-of-concept exploratory study achieved its primary aim of safety evaluation. The absence of clinically significant toxicity over 6 weeks is reassuring and aligns with the general safety profile of polyphenolic herbal infusions [25, 26, 34-37].

5. Conclusion

Daily ingestion of Genuine ESSIAC™ tea for 6 weeks was safe and well-tolerated in healthy adults, with no significant adverse laboratory findings. Mild gastrointestinal symptoms were infrequent and comparable to the known effects of the two herbal brews. Laboratory trends toward improved lipids, bilirubin, and ALP changes are mechanistically coherent with antioxidant, anti-inflammatory, and transporter-modulating actions of polyphenolic botanical constituents of both infusion and decoction. These measured variables, as well as others used in the present work, were grouped and interpreted according to distinct physiological domains, including genomic integrity, hepatic biochemistry, and lipid metabolism, rather than as a single unified efficacy endpoint. Within this framework, each outcome was treated as exploratory and intended to inform short-term safety and biological behavior under controlled exposure conditions, not to provide confirmatory evidence of efficacy. Practically, these data allowed the generation of a new hypothesis: that these infusions and decoctions may exert modest hepatoprotective and lipid-modulating effects, in addition to their genoprotective and ROS-scavenging effects; confirmation will require larger, longer-term, placebo-controlled trials with larger cohorts to assess the magnitude, durability, and therapeutic relevance of these effects.

Concluding, this study was intentionally designed as a fixed-dose, exploratory Phase I safety trial rather than a dose-escalation study. As we reported, 24 participants completed the protocol (12 per arm), which is appropriate for a closely monitored first-in-human safety assessment [28, 37]. FDA guidance describes Phase I studies as the initial introduction of an investigational product into humans, usually in healthy volunteers, and FDA guidelines note that total enrollment is generally in

the range of 20 to 80 participants; broader clinical-trial guidance likewise characterizes Phase I studies as small trials focused on safety, pharmacology, and dose selection rather than confirmatory efficacy [28]. Yerba mate was selected as an active comparator to preserve blinding and cultural acceptability, but it is not an inert placebo: human randomized data show antioxidant-related effects and an association with higher HDL-c, and experimental work has demonstrated free-radical scavenging and DNA-protective activity [25, 26].

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Author Contributions

VLMM had the primary and leading role across all stages of the project, including conceptualization, study design, oversight and execution of data collection, supervision of analyses, and manuscript preparation. LM and JLF contributed to study design, data collection, and interpretation. LM and GO carried out data collection and performed the statistical analyses. VLMM and LM prepared the first draft of the manuscript. All authors read, revised, and approved the final version.

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Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

The authors used ChatGPT (OpenAI, USA) Artificial intelligence (AI) tools solely for basic grammar correction and language refinement in the preparation of this manuscript. All scientific content, data interpretation, and conclusions were developed independently by the authors. The authors have thoroughly reviewed and edited the AI-assisted text to ensure its accuracy and accept full responsibility for the content of the manuscript, the final content was reviewed and approved by all authors.

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