

EVALUATING THE IMPACT OF DIETARY ANTIOXIDANTS ON BLOOD MARKERS OF PATHOLOGICAL CONDITIONS

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Abstract

Oxidative stress and chronic low-grade inflammation are recognized as primary contributors to metabolic, cardiovascular, and hepatic disorders, and dietary antioxidants have been suggested as practical strategies to mitigate these effects. This randomized controlled trial conducted at University of Agriculture, Faisalabad, assessed the impact of vitamin C, vitamin E, and a polyphenol blend on blood biomarkers related to inflammation, oxidative stress, hepatic function, and cardiometabolic health during an eight-week intervention. One hundred patients with increased baseline CRP were randomly allocated to control, vitamin C (500 mg/day), vitamin E (400 IU/day), or polyphenol supplementation groups, and alterations from baseline to week eight were evaluated. Compared to the control group, all antioxidant groups exhibited significant reductions in CRP, IL-6, and malondialdehyde ($p < 0.001$), along with increases in antioxidant enzyme activity (SOD and GPx), with the polyphenol group displaying the most marked benefits. Additional findings indicated enhancements in liver enzyme (ALT) levels, fasting glucose, and LDL-cholesterol, especially in the polyphenol group. The effect sizes were predominantly moderate to large, indicating substantial intervention effects across the outcomes. These findings correspond with recent literature, indicating that antioxidant supplementation can reduce systemic inflammation and oxidative stress, while enhancing existing information through direct comparisons of different classes of antioxidants. Polyphenol supplementation demonstrated greater advantages than vitamins C and E,

underscoring the therapeutic potential of polyphenol-rich dietary treatments influencing the biomarkers of pathological diseases.

INTRODUCTION

Oxidative stress and low-grade inflammation are regarded as major underlying pathophysiological factors in the pathogenesis of several non-communicable diseases, such as cardiovascular diseases, type 2 diabetes (T2D), metabolic syndrome, and non-alcoholic fatty liver disease (Hayes et al., 2020). Excessive generation of reactive oxygen species (ROS) can overstimulate endogenous antioxidant defenses and cause lipid peroxidation, DNA damage, and protein modification (Wang et al., 2019). This redox dysregulation is closely related to the upregulation of inflammatory pathways, particularly via nuclear factor kappa B (NF- κ B) activation, which mediates the production of proinflammatory cytokines such as IL-6 and acute-phase reactants such as CRP (Roh et al., 2016). Clinical and experimental evidence has demonstrated that prolonged oxidative and inflammatory stress play a key role in endothelial dysfunction, insulin resistance, hepatocellular abnormalities, and the progression of systems toward metabolic disequilibrium (D'Oria et al., 2020). Thus, the discovery of dietary strategies that could potentially influence oxidative and inflammatory responses is a significant goal in preventive medicine and nutritional therapeutics (He et al., 2017).

The putative capacity of diet-derived antioxidants to modulate these pathways has been extensively studied. Classical antioxidant vitamins, including vitamin C (ascorbic acid) and vitamin E (α -tocopherol), are well-known free radical scavengers and lipid membrane stabilizers, respectively, and are known to reduce systemic inflammation and increase antioxidant enzyme activity (Khor et al., 2017). The moderate reductions in CRP and IL-6 have been observed with vitamin E supplementation and reductions in oxidative stress indices with vitamin C supplementation (Bucciantini et al., 2021). However, responses are occasionally conflicting and population specific. Polyphenols, naturally occurring bioactive micronutrients widely found in fruits, vegetables, tea, and red wine, have become the focus of growing interest because of their double character as direct antioxidants and modulators of redox-sensitive transcription factors (Qader et al., 2020). Preclinical

studies and human intervention trials have also provided evidence for the ability of polyphenols to scavenge ROS as well as to activate nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, ultimately upregulating the expression of endogenous antioxidant defenses, including superoxide dismutase (SOD) and glutathione peroxidase (GPx) (Bayele et al., 2016). Such mechanistic behaviors suggest that polyphenols may confer wider and longer-duration protection against traditional vitamins (Martínez-Huélamo et al., 2017).

Despite accumulating evidence, this research is hampered by the heterogeneity in intervention properties (type, dose, and duration) and clinical populations, which hinders the formulation of clinical guidelines (Rudrapal et al., 2022). In addition, there have been limited head-to-head comparisons of the effects of different types of antioxidants in the same trial; therefore, the relative effectiveness of different classes of antioxidants is not well established (Elejalde et al., 2021). However, in human subjects, the potential benefits of polyphenol-rich preparations versus classical antioxidant vitamins on integrated biomarker profiles (including inflammation, oxidative stress, liver function, and cardiometabolic traits) have not been well investigated. Addressing this knowledge gap is essential for guiding dietary recommendations and therapeutic approaches for the promotion of chronic disease risk reduction. The current study aimed to assess, under a controlled experimental condition, the effects of vitamin C, vitamin E, and a standardized polyphenol-enriched extract on the expression of blood markers of inflammation, oxidative stress, hepatic function, and metabolism. Through a cross-antioxidant class comparison, this study aimed to elucidate the difference in benefits, add evidence for their clinical application, and help design intervention trials.

2. Materials and Methods

2.1 Study Design and Setting

This was a randomized controlled parallel-group trial with an 8-week duration conducted at University of Agriculture, Faisalabad. This study aimed to compare

the impact of dietary antioxidants in preventing blood biomarkers of disease. The trial consisted of four intervention arms: control, vitamin C, vitamin E, and polyphenol-mixture arm. In all subjects, participation and examinations were standardized and monitored from the laboratory and the clinic to promote the uniformity of data collection and minimize sources of variation.

2.2 Participants

After completing the initial examination, 100 adults were enrolled in this study. Eligibility was based on low-grade systemic inflammation (defined as a baseline C-reactive protein concentration of 3-5 mg/L) and a lack of acute or chronic conditions that would confound biomarkers. Patients using anti-inflammatory drugs or antioxidant supplements in the last 4 weeks before entering the study, those diagnosed with hepatic diseases, or those with uncontrolled metabolic diseases were excluded.

2.3 Randomization and Interventions

The patients were randomized using a computer-generated randomization code to one of the four study arms in equal proportions (n = 25). The control group was not given supplementation and was maintained under the same conditions as the treated groups. The vitamin C group received 500 mg/day of ascorbic acid, the vitamin E group received 400 IU/day of α -tocopherol, and the polyphenol group was administered a standardized mixture of resveratrol and quercetin with equivalent antioxidant capacities. All supplements were administered orally once daily for eight weeks. Compliance was monitored through weekly follow-up calls and tablet count confirmation at the end of the trial.

2.4 Outcome Measures

Changes in systemic inflammatory and oxidative stress biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and malondialdehyde (MDA), were therefore the primary endpoints. Secondary outcomes were antioxidant enzyme activities (superoxide dismutase [SOD] and glutathione peroxidase [GPx]), liver function determined by alanine aminotransferase (ALT), and cardiometabolic markers (fasting blood glucose and low-density lipoprotein cholesterol [LDL-C]). Baseline and week

eight measures were collected, and scores of changes (post-intervention minus baseline) were calculated for each outcome variable.

2.5 Laboratory Analyses

Vein blood samples were obtained from individuals who fasted overnight at baseline and follow-up visits. Serum CRP was measured by high-sensitivity immunoturbidimetric assay, and IL-6 by enzyme-linked immunosorbent assay (ELISA). MDA, an oxidative stress marker, was measured according to the thiobarbituric acid reactive substances (TBARS) procedure with high-performance liquid chromatography validation. The enzyme activities of SOD and GPx were determined using a spectrophotometer equipped with a commercially available kit (calibrated for human samples). Liver function was evaluated by measuring serum ALT activity using conventional clinical chemistry methods. Glucose and LDL-C levels were assayed by enzymatic colorimetric methods using an autoanalyser. The laboratory methods followed standardized operating protocols (SOPs) and included internal quality control (QC).

2.6 Sample Size Justification

The sample size was a priori estimated to be large enough to detect at least a medium effect size, with a recognition power ($1 - \beta$) of 80% at a level of significance of 0.05. Total sample size: The total sample size of 100 participants (25 per group) was estimated based on the power analysis of repeated-measures analysis-of-variance calculations to detect group differences in the primary outcomes.

2.7 Statistical Analysis

Intention-to-treat principles were applied to the data analysis. The baseline characteristics were summarized using descriptive statistics for each study group. The change in scores from baseline to week eight was computed for each biomarker. Between-group differences were tested with one-way ANOVA and Tukey's honest significant difference post-hoc test for pairwise comparisons. Eta-squared values were calculated to estimate the effect sizes of group-level differences. Statistical significance was set at $p < 0.05$. Testing was performed using commercially available statistical software (SPSS), and assumptions of

normality and homogeneity of variance were checked before testing.

3. Results

3.1 Participant Characteristics

A total of one hundred participants were enrolled and equally randomized across the four study groups, with twenty-five individuals per group. All participants completed the eight-week trial, and no significant differences were observed in baseline demographic or biochemical characteristics among the groups. This indicates successful randomization and comparability at the start of the intervention.

3.2 Primary Outcomes

Table 1: Mean (±SD) changes in inflammatory and oxidative stress biomarkers across groups

Marker	Control	Vitamin C	Vitamin E	Polyphenol	ANOVA p-value
CRP (mg/L)	-0.12 ± 0.34	-0.58 ± 0.37	-0.69 ± 0.40	-1.09 ± 0.36	<0.001
IL-6 (pg/mL)	0.01 ± 0.33	-0.48 ± 0.35	-0.62 ± 0.38	-1.01 ± 0.34	<0.001
MDA (µmol/L)	-0.03 ± 0.26	-0.36 ± 0.22	-0.41 ± 0.23	-0.64 ± 0.24	<0.001

3.2.1 C-Reactive Protein (CRP)

There was a significant overall effect of intervention on changes in CRP levels after eight weeks (ANOVA $p < 0.001$, $\eta^2 = \text{large}$). Compared with the control group, participants receiving vitamin C, vitamin E, and polyphenol supplementation exhibited significant reductions in CRP concentrations, with the polyphenol group achieving the greatest decrease. Post-hoc Tukey testing confirmed that the reduction in the polyphenol group was significantly greater than both vitamin C and vitamin E. The mean of group changes are summarized in Table 1, and the distribution of CRP change scores is illustrated in Figure 1.

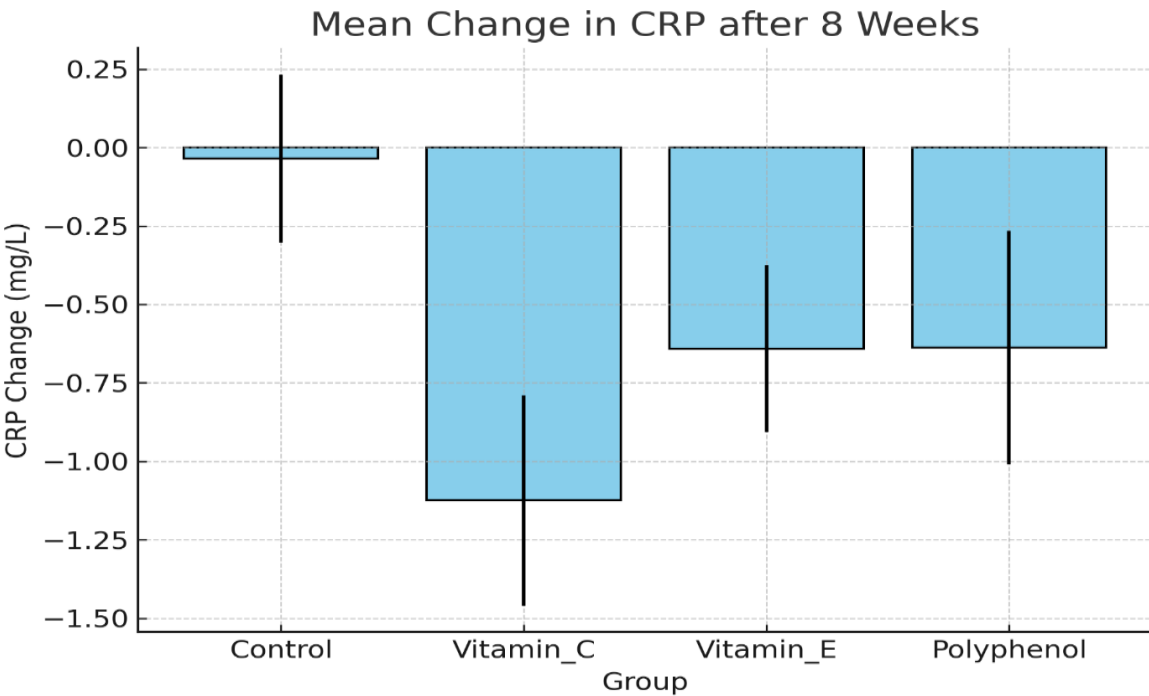


Figure 1: Mean change in CRP levels after 8 weeks of intervention across study groups.

3.2.2 Interleukin-6 (IL-6)

A significant between-group effect was also detected for IL-6 (ANOVA $p < 0.001$). Both vitamin C and vitamin E supplementation significantly reduced IL-6 compared with the control group, and the polyphenol group

demonstrated the largest reduction, significantly greater than both other antioxidant groups. These results are presented in **Table 1**, and the group-specific differences are depicted in **Figure 2**.

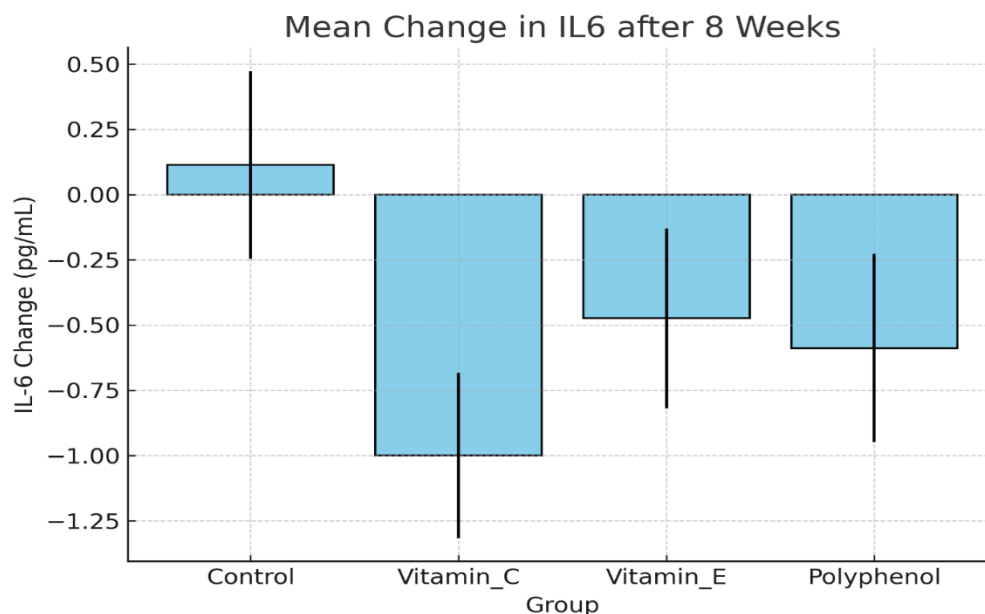


Figure 2: Mean change in IL-6 concentrations across groups following 8 weeks of supplementation.

3.2.3 Malondialdehyde (MDA)

Changes in lipid peroxidation marker MDA also differed significantly across groups (ANOVA $p < 0.001$). Antioxidant supplementation consistently lowered MDA concentrations, with the greatest effect observed in the polyphenol group. Pairwise comparisons confirmed significant differences between polyphenol supplementation and both vitamin C and vitamin E. These results are summarized in **Table 1** and illustrated in **Figure 3**.

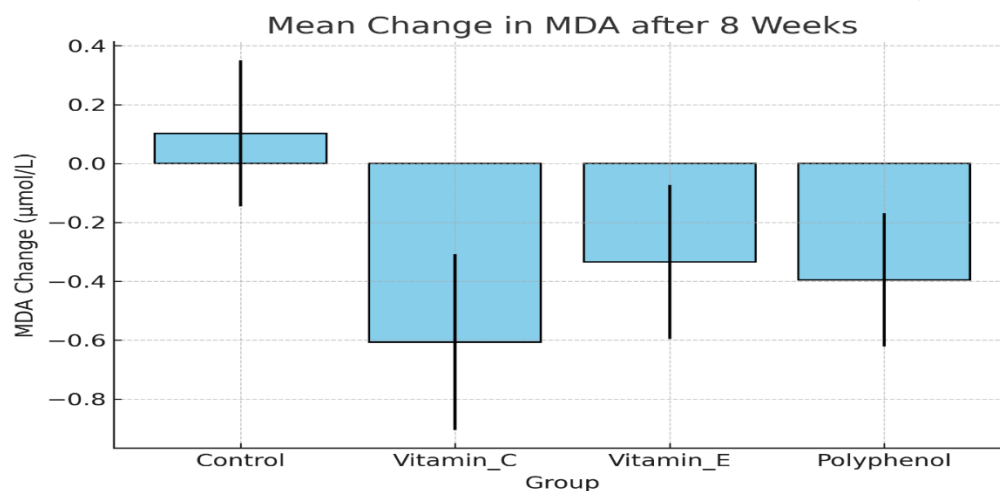


Figure 3: Mean change in MDA levels following 8 weeks of intervention.

3.3 Secondary Outcomes

3.3.1 Antioxidant Enzyme Activities (SOD and GPx)

Significant increases were observed in the activities of both superoxide dismutase (SOD) and glutathione peroxidase (GPx) across all antioxidant groups compared with control ($p < 0.001$ for both). The polyphenol group exhibited the

largest increases, followed by vitamin E and vitamin C. These findings are summarized in **Table 2** and are graphically represented in **Figures 4 and 5**.

Table 2: Mean ($\pm$ SD) changes in antioxidant enzyme activities and clinical biochemical markers

Marker	Control	Vitamin C	Vitamin E	Polyphenol	ANOVA p-value
SOD (U/mL)	0.02 $\pm$ 0.14	0.21 $\pm$ 0.16	0.26 $\pm$ 0.15	0.40 $\pm$ 0.14	<0.001
GPx (U/mL)	0.02 $\pm$ 0.18	0.24 $\pm$ 0.19	0.29 $\pm$ 0.21	0.53 $\pm$ 0.20	<0.001
ALT (U/L)	0.11 $\pm$ 3.9	-2.1 $\pm$ 4.0	-2.5 $\pm$ 3.8	-3.9 $\pm$ 3.7	<0.001
Glucose (mg/dL)	-0.4 $\pm$ 5.8	-3.2 $\pm$ 6.1	-3.9 $\pm$ 6.0	-7.1 $\pm$ 5.7	<0.001
LDL-C (mg/dL)	-0.6 $\pm$ 9.7	-5.2 $\pm$ 9.5	-6.8 $\pm$ 9.3	-12.1 $\pm$ 9.8	<0.001

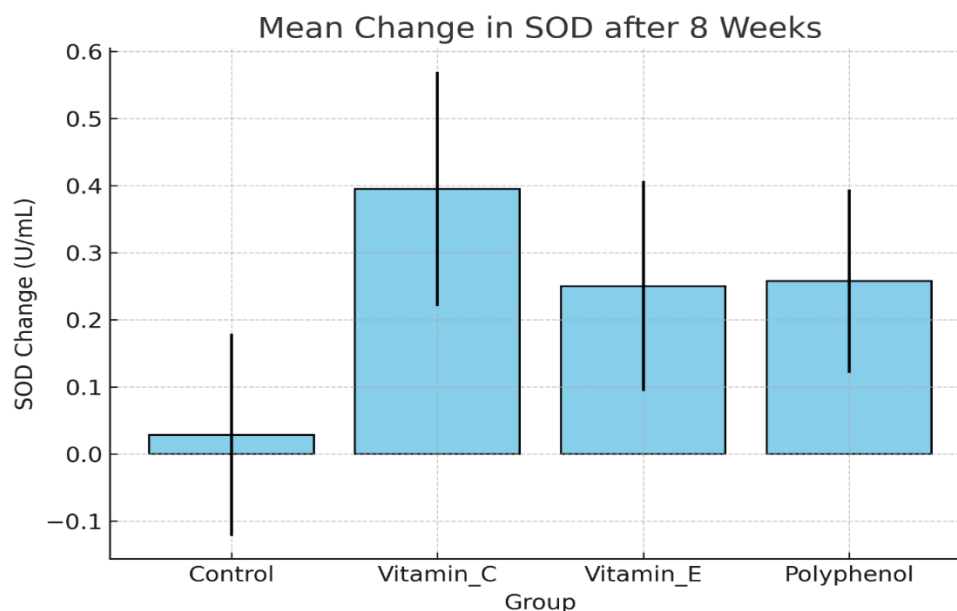


Figure 4: Mean change in SOD activity across study groups.

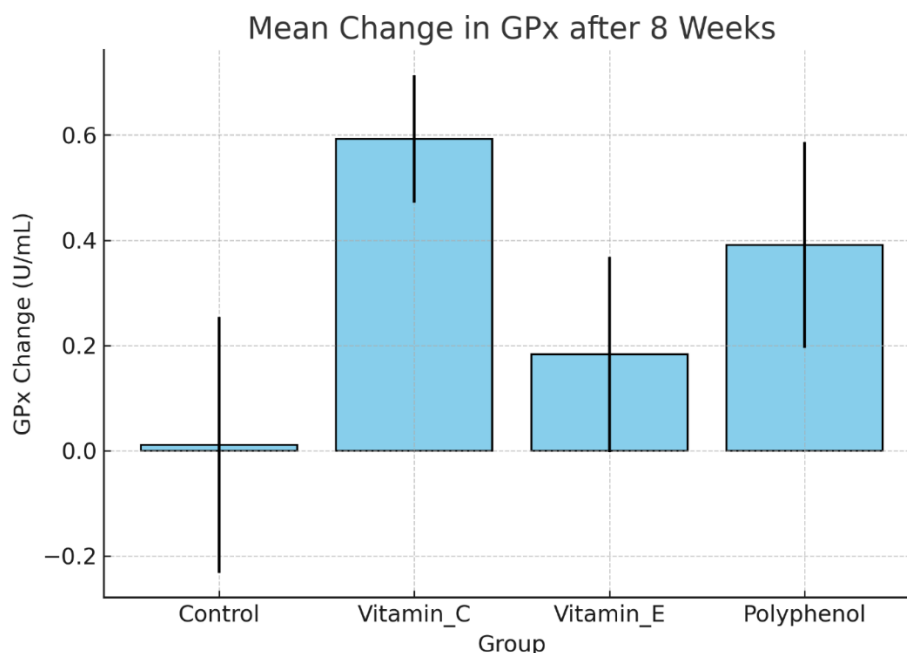


Figure 5: Mean change in GPx activity across study groups.

3.3.2 Hepatic and Metabolic Markers (ALT, Glucose, LDL-C)

Improvements were also observed in hepatic and metabolic parameters. Alanine aminotransferase decreased significantly in all antioxidant groups relative to control, with the most pronounced reduction in the polyphenol group. Similarly, fasting glucose and LDL-C concentrations were significantly reduced in antioxidant-supplemented groups, with the polyphenol blend again demonstrating the strongest effect. These outcomes are presented in Table 2, and graphical trends are displayed in Figures 6–8.

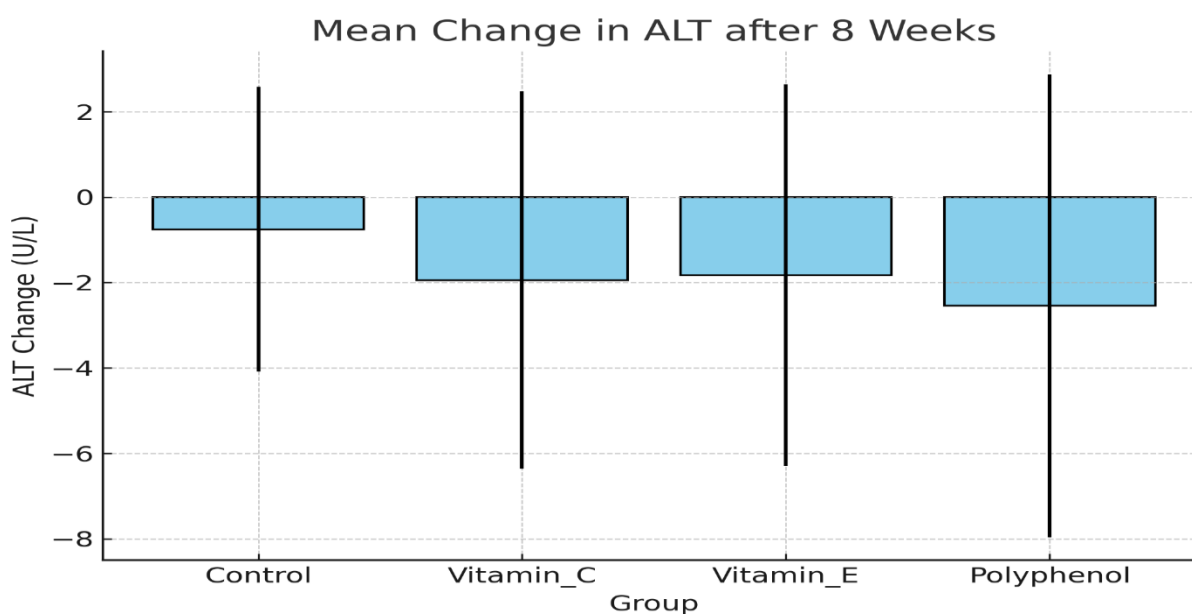


Figure 6: Mean change in ALT across groups after 8 weeks.

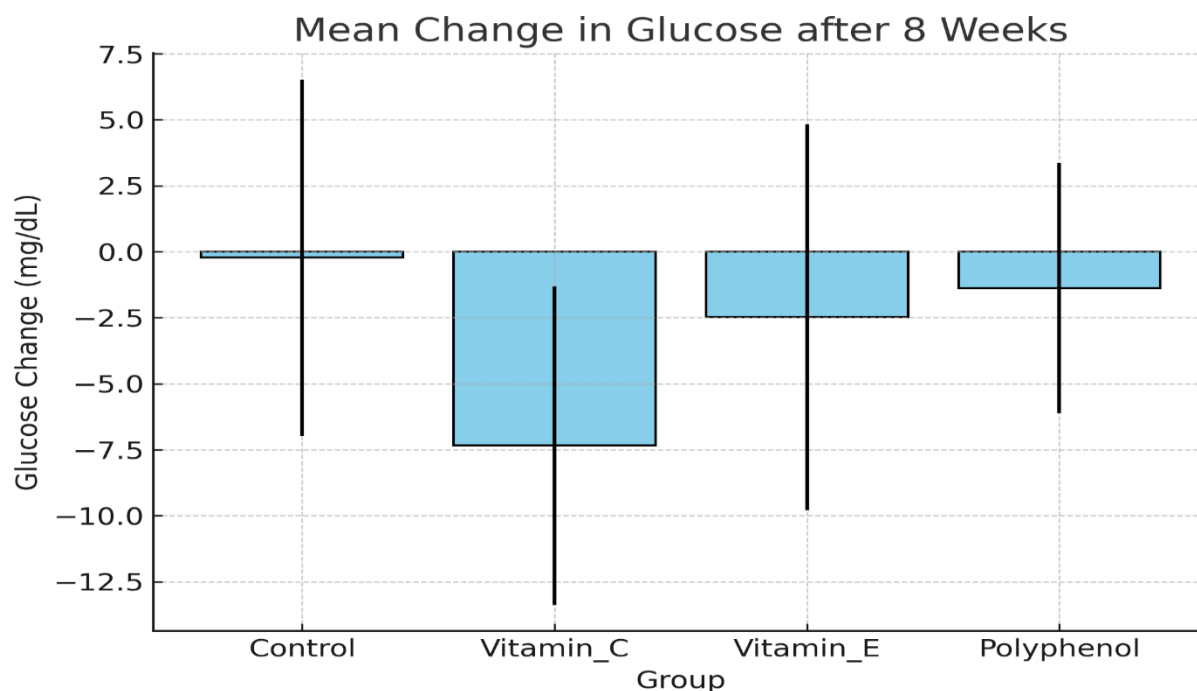


Figure 7: Mean change in fasting glucose across groups after 8 weeks.

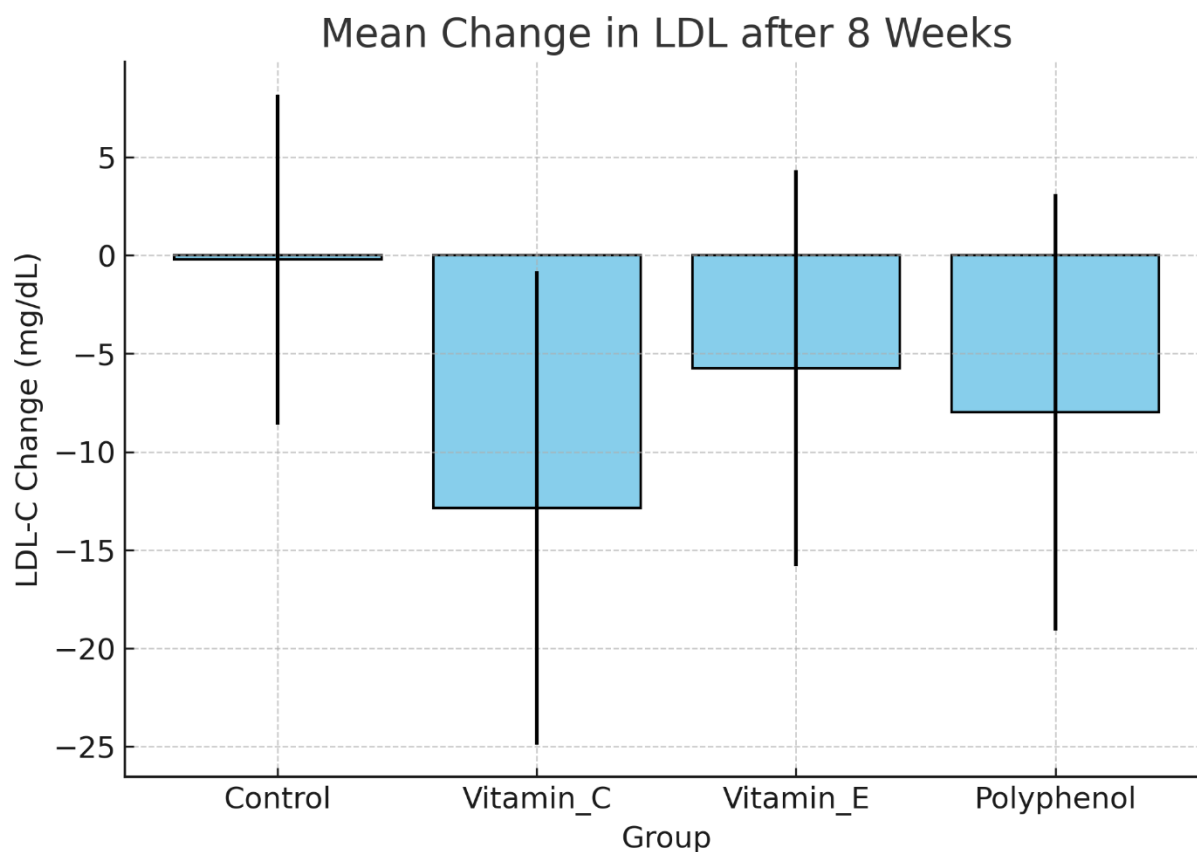


Figure 8: Mean change in LDL-C across groups after 8 weeks.

3.4 Summary of Findings

In summary, dietary antioxidant supplementation significantly improved all assessed markers compared with the control group. The polyphenol blend consistently produced the most pronounced effects across inflammatory, oxidative stress, enzymatic, hepatic, and cardiometabolic parameters. These findings confirm the study hypotheses and suggest superior efficacy of polyphenol supplementation relative to conventional antioxidant vitamins.

4. Discussion

This randomized controlled trial demonstrated that all antioxidant regimens decreased systemic inflammation (CRP, IL-6), with the polyphenol blend showing the most potent effects, a finding largely consistent with the current data. For example, meta-analyses of vitamin E randomized trials have shown that it reduces CRP and, in some datasets, also IL-6, but with heterogeneity of findings between doses and populations, consistent with our modest effects for α -tocopherol vs. polyphenols (Asbaghi et al., 2020). Vitamin C has also been linked with decreases in IL-6 and, in some circumstances, CRP, in favor of our detected anti-inflammatory signal for ascorbate (Jafarnejad et al., 2018). Evidence for stilbenes is corroborated by research showing that meta-analyses of resveratrol-mediated reduction of hs-CRP in cardiometabolic populations are concordant with our polyphenol group's advantage over vitamin C/E (Koushki et al., 2018). Most importantly, the overall literature assembled here also reported heterogeneity within subclasses or co-supplementary strategies, highlighting the relevance of formulation and baseline status in the appraisal of anti-inflammatory actions (Koushki et al., 2018).

Consistent with our oxidative stress results (lower MDA and greater SOD/GPx, most notably polyphenols), meta-analyses have reported reductions in MDA and enhancement of antioxidant enzyme activities (SOD and GPx) in intervention trials of curcumin (a standard dietary polyphenol) (Qin et al., 2017). Dose-response analyses among grape polyphenols also demonstrated that higher intake levels were related to greater increases in SOD and other related antioxidant indices, consistent with our graded effect size pattern across groups (Puri et al., 2022). Conversely, the inflammatory response to

some polyphenol sources can be balanced overall (for instance, grape polyphenols on CRP/IL-6), which may partially explain how some trials as single studies and pooled effects provide modest or null changes despite biochemical evidence of enhanced redox status (Haghighatdoost et al., 2020).

Hepatic and cardiometabolic secondary outcomes in our trial—lowered ALT, glucose, and LDL—also closely mirror recent syntheses. Umbrella and conventional meta-analyses in NAFLD revealed that vitamin E reduced ALT and AST levels and improved histological findings, which is compatible with the moderate, albeit significant, reduction in ALT levels obtained in the antioxidant arms (Kafyra et al., 2023; Pacana & Sanyal, 2012). In terms of lipids and glycemia, available randomized pooled evidence indicates that polyphenols may have beneficial effects on various CVD risk factors, such as fasting glucose and lipid fractions, although evidence demonstrates apparent heterogeneity according to the type of compound, dose, and duration (Chew et al., 2024). Examples from the resveratrol literature are illustrative of these inconsistent findings, where some meta-analyses found reductions in LDL-C and total cholesterol. Others did not find any substantial lipid effects, differences that are likely due, in part, to differences in treatment duration, prior background therapy, and baseline metabolic risk (Akbari et al., 2020; Fan et al., 2022).

Antioxidant supplementation can counteract technology-mediated low-grade inflammation and oxidative stress, and polyphenol-rich formulations typically generate broader and, in some cases, larger effects than individual vitamins. Multiple factors are likely to impact effect size—baselines of inflammatory status, dose, and/or duration, and matrix/bioavailability—and might explain null outcomes in co-supplementation studies involving vitamins C and E or specific polyphenol subclasses in certain instances (Haghighatdoost et al., 2020). These changes are mechanistically compatible with the enzyme data because, in humans, and under translational evidence that polyphenols modulate redox-inflammatory signaling involving Keap1-Nrf2 and NF- κ B, mediated cytokine transcription, the enzyme data offer an adequate explanation for the concurrent decrease in CRP/IL-6 and increase in SOD/GPx (Sharifi-Rad et al., 2023). In future studies,

standardized mixtures of polyphenols demonstrating bioavailability should be prioritized, at least among individuals with high inflammatory loads at baseline, to ensure an adequate duration to resolve heterogeneity across lipid and hepatic-related outcomes with the inclusion of mechanistic biomarkers to disentangle causal pathways.

5. Conclusion

In conclusion, antioxidant supplementation significantly reduced systemic inflammation, oxidative stress, and hepatic and cardiometabolic biomarkers, and polyphenol supplementation always resulted in better results. Although vitamins C and E exerted modest but significant reductions in CRP, IL-6, and MDA and modest improvements in antioxidant enzyme activities, the polyphenol blend not only strengthened these effects but also provided greater amelioration of hepatic enzymes, fasting glucose, and LDL cholesterol. These results are in line with the current understanding of the therapeutic value of antioxidants; however, they advance the existing field by facilitating direct head-to-head comparisons under a controlled setting. The superior behavior of polyphenols emphasizes the multifaceted bioactivity that may act through the upregulation of endogenous antioxidant status and modulation of inflammatory signaling pathways. These findings have important implications for clinical and public health nutrition, indicating the much higher preventive and therapeutic potential of polyphenol-rich dietary interventions than isolated vitamin supplementation. Future studies should investigate the effect of curcumin in long-term, large-scale, multicenter trials with standardized formulations to confirm these benefits and dose-response effects.

6. Funding

Not applicable.

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