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Effects of Algae-Based Supplementation on Metabolic, Oxidative, and Inflammatory Markers in Physically Active Adults: A Pilot Randomized Controlled Trial

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Abstract: Algae-based supplements are gaining attention for their potential metabolic, antioxidant, and anti-inflammatory properties in sports nutrition. **Methods:** A 30-day pilot randomized controlled trial was conducted in 70 healthy male athletes (mean age 25.4 ± 4.9 years) from competitive soccer and handball teams. Participants were randomly assigned to a supplementation group (6 g/day of *Ulva*-derived algae powder) or a control group. Both groups followed identical training routines and adhered to standardized nutritional recommendations, including macronutrient distribution and permitted supplements (e.g., isotonic drinks, protein shakes). Biochemical markers analyzed at baseline and post-intervention included HbA1c, lipid profile, malondialdehyde (MDA), catalase, myeloperoxidase (MPO), erythrocyte sedimentation rate (ESR), and cortisol. Genetic polymorphisms related to metabolic traits were also assessed. **Results:** Significant group × time interactions ($p < 0.001$) were observed for HbA1c, LDL, triglycerides, MDA, MPO, ESR, and cortisol, all of which improved in the algae-supplemented group. Correlation analysis revealed associations between HbA1c and LDL/TG as well as between cortisol and MPO. No significant genetic modulation of responses was detected, although a trend was noted for cortisol variation and insulin resistance risk. **Conclusions:** Algae-based supplementation led to favorable metabolic, oxidative, and inflammatory changes. These findings suggest its potential utility as a nutritional strategy to support recovery in athletes during periods of high training load or competition.

Keywords: algae-based supplement; metabolic health; oxidative stress; inflammation; physically active adults; randomized controlled trial

1. Introduction

The use of marine algae-derived supplements has gained increasing attention in sports nutrition due to their potential to support metabolic regulation, counteract oxidative stress, and modulate inflammatory pathways. Among these, *Ulva* spp. has emerged as a promising candidate because of its rich content of bioactive compounds such as sulfated polysaccharides (ulvans), polyphenols, minerals, antioxidants, and highly bioavailable proteins [1–3]. These constituents have demonstrated various physiological effects in preclinical models, suggesting that Ulva-based supplementation may benefit physically active individuals.

One of the most notable bioactive components in Ulva is ulvan, a sulfated polysaccharide that has demonstrated antihyperglycemic effects, improving insulin tolerance and enhancing antioxidant enzyme activity, which can contribute to better blood glucose control [2]. Additionally, ulvans from Ulva have exhibited gut microbiota-modulating properties, which may further support metabolic regulation and gastrointestinal health—key aspects in sports performance and recovery [3].

Beyond polysaccharides, Ulva is also rich in soluble and insoluble fibers, which have been linked to improvements in carbohydrate metabolism and lipid profiles [4]. These dietary fibers not only support gut health but also contribute to lower cholesterol levels and improved lipid metabolism, both of which are essential for sustaining energy levels in physically active individuals. Given these findings, the integration of *Ulva*-derived supplements in sports nutrition presents an opportunity to enhance metabolic efficiency and performance in athletes.

Intense physical activity increases the production of reactive oxygen species (ROS), which, if not adequately neutralized, can lead to oxidative stress, cellular damage, and reduced performance [5]. Elevated oxidative stress has been associated with muscle fatigue, tissue damage, and longer recovery times [6].

Marine algae, including Ulva, contain potent antioxidants such as polyphenols, flavonoids, carotenoids, and sulfated polysaccharides, which have demonstrated strong free radical scavenging activity and the ability to enhance endogenous antioxidant defenses [7]. A recent meta-analysis on algal-based supplements found significant reductions in oxidative stress markers and improvements in antioxidant enzyme activity, further supporting their potential role in sports performance and recovery [8].

Beyond oxidative stress, prolonged high-intensity training can also lead to chronic inflammation, which may interfere with muscle regeneration and increase the risk of injuries. Markers such as myeloperoxidase (MPO) and the erythrocyte sedimentation rate (ESR) are widely used to assess inflammatory status in athletes [9]. While certain Ulva extracts have demonstrated immunomodulatory properties, their effects on inflammation markers in physically active populations remain unclear [10].

Although the effects of marine algae have been reported in animal models and populations with metabolic disorders [11] few studies have evaluated these effects in athletes, a population exposed to high metabolic demands, redox imbalance, and chronic inflammatory load. This gap in the literature represents a major limitation in applying current findings to real-world sports contexts.

In addition, the potential of algae-based supplementation to support recovery, enhance metabolic efficiency, and reduce inflammation has not been clearly validated using randomized controlled trials in elite or highly trained individuals. Such knowledge is highly relevant for coaches, sports nutritionists, and athletes interested in functional strategies to support adaptation to training and prevent performance declines during intense periods [12].

This study aimed to evaluate the effects of a marine algae-based supplement derived from Ulva on glycemic control, lipid metabolism, oxidative stress, and inflammatory responses in athletes. By assessing these key physiological parameters, the present study aims to provide evidence on the potential of algae-derived supplementation as a natural strategy to support recovery, metabolic regulation, and physiological resilience in physically active populations. The findings may contribute to the development of evidence-based nutritional interventions in sports contexts.

2. Materials and Methods

2.1. Supplement Characteristics

The supplement used in the intervention consisted of a powdered extract derived from *Ulva* spp., a green macroalga selected for its high content of bioactive compounds. The extract was provided in individual sachets containing 6 g of freeze-dried powder, and participants in the intervention group consumed one sachet daily for 30 consecutive days.

The antioxidant capacity of the extract was determined using the Trolox equivalent antioxidant capacity (TEAC) assay, yielding a value of 490 $\pm$ 4 mg Trolox/kg of dry matter. The total polyphenol content, expressed as gallic acid equivalents (GAE), was 2070 $\pm$ 80 mg GAE/kg, indicating a high concentration of antioxidant phytochemicals.

The nutritional composition of the algae-based powder (per 100g of dry matter) was as follows: <0.5 g sugars, 0.90 g total fat (of which 0.40 g were saturated), 12.6 g carbohydrates, 23.0 g fiber, 16.8 g protein, and 14.0 g salt, providing a total energy value of 172 kcal (720 kJ). This profile reflects a low sugar and fat content, moderate protein content, and a notably high fiber content.

2.2. Study Design and Participants

This pilot randomized controlled trial was conducted to evaluate the effects of algae-based supplementation on metabolic parameters, oxidative stress, inflammatory biomarkers, and physical performance in athletes over a 30-day intervention period. Participants were randomly assigned to one of two groups: a supplementation group, which consumed 6 g/day of a powdered extract derived from *Ulva* spp., or a control group, which did not receive any supplement. Both groups followed standardized nutritional and supplementation guidelines aligned with current sports nutrition recommendations. These included individualized targets for carbohydrate (5–7 g/kg/day), protein (1.6–2.2 g/kg/day), and fat intake (approximately 1 g/kg/day), as well as ensuring adequate intake of micronutrients based on dietary reference values. Regarding supplementation, all participants were encouraged to consume isotonic drinks for hydration and protein shakes post-exercise, which are common practices among athletes, and this practice was maintained throughout the intervention to avoid introducing confounding variables.

A total of 70 male athletes aged 18 years or older were recruited from elite soccer and handball teams through collaboration agreements with their coaching and medical staff. All participants competed at the national level and were actively engaged in structured training programs comprising at least four sessions per week, including technical, tactical, and strength-conditioning work. To be considered for the study, athletes had to have a minimum of 3 years of continuous training experience in their respective sports.

Inclusion criteria required participants to (i) be healthy and physically active males; (ii) have no chronic illnesses (e.g., diabetes, hypertension, cardiovascular disease); (iii) be free from musculoskeletal injuries or surgeries in the last 6 months; (iv) have maintained stable body weight ($\pm$2 kg) for the previous 3 months; and (v) have refrained from using supplements or medications known to affect metabolism, inflammation, or oxidative stress. Exclusion criteria included the following: (i) current smoking, (ii) following special or

restrictive diets (e.g., ketogenic, vegan); (iii) recent participation in other clinical studies; or (iv) known intolerance to seaweed or algae-based products.

Participants were randomly allocated using a computer-generated simple randomization procedure, resulting in 35 athletes per group. The study did not include placebo administration or blinding. This decision was not aimed at improving perceived efficacy, but rather at preserving the natural routines of the control group. The inclusion of a placebo might have altered behavior or adherence patterns, potentially confounding biochemical results. To reduce this risk and maintain protocol consistency, both groups received the same dietary guidance and were monitored regularly throughout the study.

2.3. Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of University of Alicante (UA-2021-03-11). All participants provided written informed consent before enrollment. Participation was voluntary, and confidentiality was maintained throughout the study.

2.4. Variables Included

To evaluate the impact of algae-based supplementation on metabolic health, oxidative stress, and inflammation, the following biochemical and physiological variables were assessed at baseline (pre-intervention) and after 30 days (post-intervention).

2.4.1. Genetic Analysis

Furthermore, a genetic analysis was conducted to assess individual predisposition to metabolic and inflammatory responses. For this purpose, the N-GENE.AI digital platform (https://app.n-gene.ai; accessed on 1 May 2025) was employed to analyze selected genetic polymorphisms. The platform utilizes DNA profiling to generate predictive insights into metabolic efficiency, oxidative balance, and inflammation-related pathways. Participants provided a saliva sample, which was processed for genotyping according to the provider's validated protocol.

All biochemical markers were analyzed under fasting conditions, with blood samples collected in the early morning to minimize variability due to circadian fluctuations. Laboratory analyses were performed using standardized and validated procedures, ensuring accuracy and reproducibility of results across time points.

2.4.2. Metabolic Variables

Metabolic function was evaluated by measuring glycated hemoglobin (HbA1c, %), which serves as an integrated marker of long-term glycemic control and insulin sensitivity. Additionally, a comprehensive lipid profile was determined, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride concentrations (mg/dL), providing insights into cardiovascular and metabolic status.

2.4.3. Oxidative Stress and Antioxidant Markers

To assess oxidative stress, two key markers were analyzed. Malondialdehyde (MDA, nmol/L), a byproduct of lipid peroxidation, was used as a biomarker of cellular oxidative damage. In parallel, catalase activity (U/mg protein) was measured as an indicator of endogenous antioxidant defense capacity. Together, these markers reflect the redox balance and oxidative status of the participants during the intervention.

2.4.4. Inflammatory and Hormonal Markers

Inflammatory status and hormonal response were evaluated using myeloperoxidase (MPO, U/L), an enzyme implicated in both inflammation and oxidative mechanisms, as

well as the erythrocyte sedimentation rate (ESR, mm/h), a non-specific but widely used indicator of systemic inflammation. In addition, cortisol (μg/dL) levels were quantified to capture the physiological stress response, given its role in energy metabolism and catabolic processes during physical exertion.

2.5. Statistical Analysis

All statistical analyses were performed using JAMOVI statistical software (version 2.6.17.0, Sydney, Australia). Data distribution was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated with Levene's test. To determine the effects of algae-based supplementation, a two-way repeated-measures ANOVA (2 × 2) was conducted with group (supplement vs. control) and time (pre- vs. post-intervention) as factors. When a significant group × time interaction was detected, Bonferroni-corrected post hoc comparisons were applied to explore within- and between-group differences.

For variables that did not meet normality assumptions, non-parametric tests were used: the Wilcoxon signed-rank test for within-group comparisons and the Mann–Whitney U test for between-group comparisons. Statistical significance was set at $p < 0.05$. Results are expressed as mean ± standard deviation (SD).

In addition to analyzing absolute values, all outcome variables were normalized to baseline values, and percentage changes from baseline were calculated for each participant. These relative changes were compared between groups to enhance statistical robustness and account for inter-individual variability.

To explore potential gene–outcome interactions, one-way ANOVA (Welch's test) was applied using genetic variants as grouping factors, with either baseline values or percentage change as dependent variables. Although no significant associations were observed, these exploratory analyses aimed to identify potential genotype–phenotype relationships.

Finally, Spearman correlation analyses were conducted to examine associations among metabolic, inflammatory, and oxidative stress markers, providing insight into the interconnected nature of physiological responses to the intervention.

3. Results

A total of 70 athletes completed the pilot clinical trial. Participants were randomly and evenly allocated to the intervention group (receiving the algae-based supplement) or the control group, with 35 individuals in each. The mean age was 25.4 ± 4.91 years in the intervention group and 25.3 ± 5.19 years in the control group. No statistically significant differences were observed between groups at baseline in terms of age, height, weight, or BMI ($p > 0.05$), supporting the homogeneity of the sample and enabling valid comparisons throughout the intervention period (Table 1).

Table 1. Baseline characteristics of participants in the algae supplement and control groups.

	Algae Supplement Group			**Control Group**			***t* Test (Student's)**		
	Mean		**Ds**	**Mean**		**Ds**	***p***	**MD**	**ES (Cohen's d)**
Age (years)	25.4	±	4.9	25.3	±	5.2	0.888	0.171	0.0339
Height (cm)	186.0	±	6.2	187.0	±	6.5	0.924	−0.146	−0.0229
Weight (kg)	91.8	±	10.8	85.9	±	20.9	0.140	5.923	0.3568
BMI (kg/m^2)	26.4	±	2.91	24.8	±	6.29	0.176	1.603	0.3271

DS, standard deviation; MD, mean difference; ES, effect size (Cohen's d); BMI, body mass index; cm, centimeters; kg, kilograms; m, meters.

3.1. Genetic Profile

A genetic analysis was conducted to evaluate participants' predisposition to metabolic alterations, inflammatory status, neuromuscular regulation, and nutrient intolerance. The objective was to assess the distribution of key genetic variants and explore whether baseline genetic predispositions could modulate the physiological response to algae-based supplementation.

The analysis included variants related to anxiety, dopamine regulation, appetite control, sugar addiction, systemic inflammation, insulin resistance, metabolic syndrome, and intolerances to gluten, lactose, and fructose. Additionally, predisposition to vitamin D and B12 deficiencies and blood clotting risk were assessed.

Table 2 shows the absolute and relative frequency distributions of genetic profiles across both groups. A chi-square test was used to evaluate between-group differences in genotype frequencies. No statistically significant differences were observed between the intervention and control groups for any of the polymorphisms analyzed ($p > 0.05$), suggesting that the groups were genetically comparable at baseline. This supports the internal validity of the trial by minimizing the likelihood that genetic variation confounded the observed intervention effects.

Table 2. Distribution of gene frequencies.

Variable	Category	Algae Supplement Group, n (%)	Control Group, n (%)
Anxiety	Low	13 (18.6%)	12 (17.1%)
	Average	8 (11.4%)	7 (10.0%)
	Protected	14 (20.0%)	16 (22.9%)
Dopamine	Low	11 (15.7%)	13 (18.6%)
	Average	8 (11.4%)	8 (11.4%)
	Protected	16 (22.9%)	14 (20.0%)
Appetite	Low	7 (10.0%)	9 (12.9%)
	Average	17 (24.3%)	17 (24.3%)
	Protected	11 (15.7%)	9 (12.9%)
Sugar Addiction Predisposition	Low	9 (12.9%)	10 (14.3%)
	Average	11 (15.7%)	13 (18.6%)
	Protected	15 (21.4%)	12 (17.1%)
Inflammation Predisposition	Low	10 (14.3%)	8 (11.4%)
	Low/Average	9 (12.9%)	9 (12.9%)
	Average	16 (22.9%)	18 (25.7%)
Insulin Resistance	Average	19 (27.1%)	18 (25.7%)
	Protected	16 (22.9%)	17 (24.3%)
Metabolic Syndrome	Average	22 (31.4%)	20 (28.6%)
	At risk	7 (10.0%)	9 (12.9%)
	Protected	6 (8.6%)	6 (8.6%)
Gluten Intolerance	At risk for celiac disease	16 (22.9%)	16 (22.9%)
	No risk haplotypes	19 (27.1%)	19 (27.1%)

Table 2. *Cont.*

Variable	Category	Algae Supplement Group, n (%)	Control Group, n (%)
Lactose Intolerance	High risk	3 (4.3%)	1 (1.4%)
	Low risk	20 (28.6%)	21 (30.0%)
	Medium risk	12 (17.1%)	13 (18.6%)
Fructose Intolerance	Low risk	28 (40.0%)	27 (38.6%)
	Medium risk	7 (10.0%)	8 (11.4%)
Blood Clot Risk	Average	21 (30.0%)	21 (30.0%)
	At risk	5 (7.1%)	5 (7.1%)
	Protected	9 (12.9%)	9 (12.9%)
Vitamin D Levels	Average	15 (21.4%)	15 (21.4%)
	High levels	6 (8.6%)	5 (7.1%)
	Low levels	14 (20.0%)	15 (21.4%)
Vitamin B12 Levels	Average	14 (20.0%)	17 (24.3%)
	High levels	11 (15.7%)	8 (11.4%)
	Low levels	10 (14.3%)	10 (14.3%)

Values are expressed as absolute frequencies and percentages (%), where the percentage indicates the proportion of participants within each group who presented a given genetic category. No significant differences were observed between groups in the distribution of any genotype ($p > 0.05$ for all comparisons, chi-square test).

To assess the potential influence of genetic predisposition on the variability of metabolic, oxidative, and inflammatory markers, a series of one-way ANOVA tests were conducted using each genetic variable as a grouping factor. No statistically significant associations ($p > 0.05$) were found between any of the genetic categories and the baseline levels of biochemical markers such as HbA1c, lipid profile (HDL, LDL, triglycerides), malondialdehyde, catalase, myeloperoxidase, or erythrocyte sedimentation rate. However, a trend toward significance was observed for cortisol levels in relation to genetic predisposition to insulin resistance ($F = 3.97$, $p = 0.050$), suggesting a potential influence of this genotype on stress-related hormonal regulation. While this finding did not reach the conventional threshold for statistical significance, it may warrant further investigation in future studies with larger samples.

3.2. Metabolic Variables

Table 3 shows the mean and standard deviation values of metabolic variables (HbA1c, HDL, LDL, and TG) in both groups before and after the intervention. Additionally, results from the repeated-measures ANOVA are presented, including the main effect of time and the time × group interaction.

A significant group × time interaction was observed for HbA1c ($F(1,72) = 1351.57$, $p < 0.001$, $\eta^2_p = 0.952$), indicating a differential effect between groups over time. Post hoc analyses confirmed a significant reduction in HbA1c in the algae-based supplement group ($p < 0.001$), while the control group showed a significant increase ($p < 0.001$). The between-group difference at post-intervention was also statistically significant ($p < 0.001$).

Similarly, a significant interaction effect was found for LDL cholesterol ($F(1,68) = 6893.35$, $p < 0.001$, $\eta^2_p = 0.990$). Post hoc tests revealed a significant decrease in LDL levels in the algae-based supplement group ($p < 0.001$) and a slight, non-significant increase in the control group. The between-group difference at post-intervention was significant ($p < 0.001$).

Table 3. Pre- and post-intervention values of metabolic variables in both groups and results of repeated-measures ANOVA.

	Algae Supplement Group				Control Group				ANOVA					
	PRE		POST		PRE		POST		Effect Time			Effect Time × Group		
	Mean	Ds	Mean	Ds	Mean	Ds	Mean	Ds	F	*p* Value	η^2_p	F	*p* Value	η^2_p
HbA1C (%)	5.07	± 0.38	4.83	± 0.37	5.11	± 0.32	5.35	± 0.34	1.72	0.194	0.025	1351.57	<0.001	0.952
HDL (mg/dL)	61.40	± 6.50	58.30	± 6.17	59.80	± 6.07	62.70	± 6.37	1.280	0.261	0.019	6344.15	<0.001	0.989
LDL (mg/dL)	93.20	± 9.19	88.60	± 8.73	93.50	± 9.36	98.20	± 9.83	0.003	0.960	0.000	6.893	<0.001	0.990
TG (mg/dL)	70.70	± 15.00	67.10	± 14.20	73.70	± 15.60	77.40	± 16.40	0.455	0.502	0.007	1.575	<0.001	0.959

F and *p* values refer to the results of the repeated-measures ANOVA for the main effect of time and the time × group interaction. η^2_p: partial eta squared (effect size). HbA1c: glycated hemoglobin. HDL: high-density lipoprotein cholesterol. LDL: low-density lipoprotein cholesterol. TG: triglycerides. F: F statistic. *p*: *p*-value. η^2_p: partial eta squared. SD: standard deviation.

Triglycerides (TGs) also showed a significant group × time interaction (F(1,68) = 1574.76, $p < 0.001$, $\eta^2_p = 0.959$). While the algae-based supplement group experienced a notable reduction ($p < 0.001$), the control group showed an increase, with a significant difference observed between groups at post-intervention ($p = 0.041$).

Finally, for HDL cholesterol, the interaction effect was significant though with a smaller effect size (F(1,68) = 6344.15, $p < 0.001$, $\eta^2_p = 0.989$). Post hoc comparisons showed a decrease in HDL levels in the algae-based supplement group and an increase in the control group. The between-group difference post-intervention was significant ($p = 0.026$), although the clinical interpretation may require caution due to the divergent nature of the response.

3.3. Oxidative Stress and Antioxidant Markers

The results of oxidative stress markers are shown in Figures 1 and 2. A significant time × group interaction was observed for malondialdehyde (MDA) concentrations (F(1,68) = 213.80, $p < 0.001$, $\eta^2_p = 0.759$). Post hoc analysis revealed that MDA levels significantly decreased in the algae-based supplement group (from 1.41 ± 0.38 to 1.31 ± 0.37 nmol/mL, $p < 0.001$), while they increased in the control group (from 1.43 ± 0.27 to 1.49 ± 0.29 nmol/mL, $p < 0.001$). These opposing trends suggest a relevant effect of algae supplementation in attenuating exercise-induced lipid peroxidation.

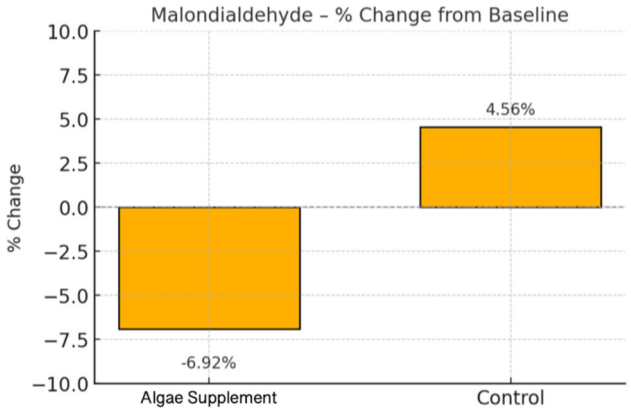

Figure 1. Percentage change in malondialdehyde (MDA) concentrations from baseline after 30 days of intervention.

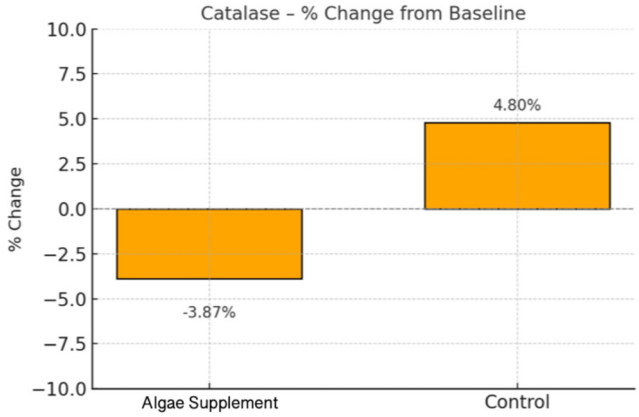

Figure 2. Percentage change in catalase activity from baseline after 30 days of intervention.

A similar interaction was observed for catalase activity, another oxidative stress-related marker ($F(1,68) = 52.31$, $p < 0.001$, $\eta^2_p = 0.435$). In the algae-supplemented group, catalase levels decreased (from 49.00 ± 5.53 to 47.20 ± 5.25 kU/L), while the control group exhibited a significant increase (from 51.80 ± 6.06 to 54.30 ± 6.36 kU/L). Although a reduction in catalase might initially appear counterintuitive, it may reflect a lower oxidative burden and, thus, a diminished need for endogenous antioxidant compensation.

3.4. Inflammatory and Hormonal Markers

A significant time × group interaction was found for myeloperoxidase (MPO) levels ($F(1,68) = 1296.75$, $p < 0.001$, $\eta^2_p = 0.950$), indicating a divergent pattern of change between groups (Table 4). Post hoc tests revealed a significant reduction in MPO levels in the algae-supplemented group from baseline to post-intervention ($p < 0.001$), whereas changes in the control group were not significant ($p = 0.577$). The between-group difference at post-intervention did not reach statistical significance ($p = 0.181$), although the trend favored the experimental group.

Table 4. Pre- and post-intervention values of inflammatory and hormonal markers in both groups and results of repeated-measures ANOVA.

	Algae Supplement Group				**Control Group**				**ANOVA**					
	PRE		**POST**		**PRE**		**POST**		**Effect Time**			**Effect Time × Group**		
	Mean	**Ds**	**Mean**	**Ds**	**Mean**	**Ds**	**Mean**	**Ds**	**F**	***p* Value**	**η^2_p**	**F**	***p* Value**	**η^2_p**
MPO (ng/mL)	55.20	± 12.20	52.50	± 11.60	49.00	± 12.10	51.50	± 12.70	4.55	0.036	0.063	1296.75	<0.001	0.950
Cortisol (µg/dL)	15.80	± 5.68	15.00	± 5.40	13.40	± 5.83	14.10	± 6.12	3.02	0.087	0.043	450.05	<0.001	0.869
ESR (mm/h)	5.67	± 2.48	5.38	± 2.36	4.43	± 3.12	4.43	± 3.27	12.1	<.001	0.152	85.8	<0.001	0.558

F and *p* values refer to the results of the repeated-measures ANOVA for the main effect of time and the time × group interaction. η^2_p: partial eta squared (effect size). MPO: myeloperoxidase. ESR: Erythrocyte sedimentation rate. F: F statistic. *p*: *p*-value. η^2_p: partial eta squared. SD: standard deviation.

Regarding cortisol, the analysis also showed a significant group × time interaction ($F(1,68) = 450.05$, $p < 0.001$, $\eta^2_p = 0.869$). Post hoc comparisons confirmed a significant decrease in cortisol levels in the algae-supplemented group ($p < 0.001$), contrasting with a modest, non-significant increase in the control group. No significant between-group differences were observed at baseline or at post-intervention ($p > 0.90$).

Finally, for the erythrocyte sedimentation rate (ESR), a significant interaction was detected ($F(1,68) = 85.8$, $p < 0.001$, $\eta^2_p = 0.558$). The algae-supplemented group experienced

a marked decrease ($p < 0.001$), while the control group exhibited a moderate increase ($p < 0.001$). The post-intervention comparison between groups approached significance ($p = 0.125$).

3.5. Correlations

Significant positive correlations (Figure 3) were observed between HbA1c and both LDL (ρ = 0.357, $p = 0.002$) and triglycerides (ρ = 0.340, $p = 0.004$), indicating that impaired glycemic control was associated with a worsened lipid profile. LDL and triglycerides also showed a strong correlation (ρ = 0.432, $p < 0.001$). Moreover, cortisol levels were positively correlated with myeloperoxidase (ρ = 0.255, $p = 0.034$), suggesting a link between stress response and inflammatory activity. HDL was positively associated with catalase activity (ρ = 0.243, $p = 0.042$), reflecting the interaction between lipid metabolism and antioxidant defense.

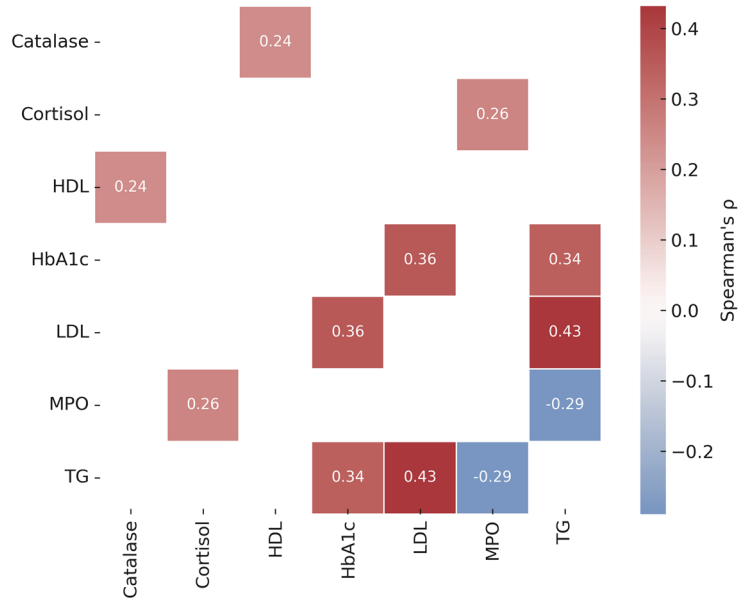

Figure 3. Significant Spearman correlations between biochemical and physiological biomarkers. Only statistically significant associations ($p < 0.05$) are presented. The color scale represents the direction and strength of the correlation (ρ), with positive correlations shown in red and negative correlations in blue. Correlation coefficients are based on non-parametric Spearman analysis. HbA1c: glycated hemoglobin. LDL: low-density lipoprotein cholesterol. HDL: high-density lipoprotein cholesterol. TG: triglycerides. MPO: myeloperoxidase.

4. Discussion

This pilot clinical trial demonstrates that 30-day supplementation with an *Ulva*-derived powdered extract leads to significant improvements in metabolic, oxidative, and inflammatory markers in physically active individuals. These findings contribute to the growing body of evidence supporting the use of marine algae extracts in functional nutrition, especially in the context of recovery and metabolic regulation in athletes.

From a metabolic standpoint, significant reductions in HbA1c, LDL cholesterol, and triglycerides were observed in the algae-supplemented group. These results align with prior studies highlighting the antihyperglycemic effects of Ulva polysaccharides, attributed to their fiber and ulvan content, which can modulate glycemic response and insulin sensitivity [3,13]. Additionally, Taboada et al. [13] and Wang et al. [14] reported lipid-lowering effects of Ulva via enhanced bile acid excretion. Supporting this, a recent meta-analysis by Pishva Arzhang et al. [11] involving 77 randomized trials confirmed that algae supplementation significantly reduced total cholesterol, LDL, and triglycerides, particularly in

short-term interventions (≤10 weeks). These data reinforce the lipid-modulating potential of algae.

The intervention also influenced oxidative stress and inflammation. A decrease in malondialdehyde (MDA) and modulation of catalase activity were observed, consistent with the antioxidant profile of *Ulva* spp., rich in polyphenols and sulfated polysaccharides [1,15]. Inflammatory biomarkers such as MPO and ESR were also reduced, supporting the known immunomodulatory properties of Ulva, as previously shown in vitro [16].

Moreover, a significant decrease in cortisol levels suggests that algae supplementation may attenuate stress responses, potentially due to adaptogenic properties. This is particularly relevant for athletes under high training loads, where cumulative stress and inflammation can impair performance and recovery [17,18].

While these effects may not be surprising biochemically, they hold valuable practical implications for sports professionals. The reductions observed in HbA1c, LDL, TG, MDA, MPO, ESR, and cortisol point to improved recovery and stress regulation. Therefore, algae supplementation may serve as a supportive nutritional strategy during periods of intensified training or competition.

Correlational analyses revealed significant associations between glycemic and lipid markers (e.g., HbA1c and LDL, HbA1c and TG) as well as between inflammatory and oxidative markers (e.g., cortisol and MPO, HDL and catalase), highlighting the interconnectedness of metabolic and redox pathways. These findings align with the concept of integrative metabolic regulation, where interventions targeting one axis (e.g., oxidative stress) may have downstream benefits across systems.

While the observed effects may not be unexpected from a biochemical perspective, the findings offer meaningful practical implications for sports practitioners and nutrition professionals. The intervention led to significant reductions in HbA1c, LDL, TG, MDA, MPO, ESR, and cortisol—biomarkers linked to metabolic health, recovery, and stress adaptation. These improvements suggest that algae-based supplementation could serve as a supportive nutritional strategy for athletes exposed to high training loads or congested competition periods, where controlling inflammation, oxidative stress, and metabolic strain is critical.

Genetic analyses revealed no significant differences between groups at baseline and no major genotype–phenotype interactions, although a near-significant effect was observed for cortisol and insulin resistance polymorphisms, warranting further study.

This study presents some limitations. Firstly, the intervention period was relatively short (30 days), and although significant changes in biochemical markers were observed, long-term outcomes—particularly those related to physical performance or clinical endpoints—remain to be investigated. Secondly, although the sample size was appropriate for a pilot trial, it limits the generalizability of the findings and reduces the ability to detect subtle genotype–phenotype interactions. Additionally, the absence of a placebo control group must be acknowledged. This decision was intentional, as the introduction of a placebo could have altered the behavior or dietary adherence of the control group, potentially confounding the biochemical outcomes. While this approach preserved ecological validity, it limited the capacity to fully isolate potential placebo effects. Future studies should address these limitations by including larger and more heterogeneous populations, implementing placebo-controlled designs, and incorporating dose–response assessments to further explore the efficacy and mechanistic pathways of algae-based supplementation.

5. Conclusions

Thirty days of supplementation with an *Ulva*-derived algae-based product resulted in significant improvements in glycemic control, lipid profile, oxidative stress, and hormonal

regulation in physically active individuals. These findings support the potential of algae-based supplements as effective nutritional strategies to enhance metabolic health and recovery in athletic populations. Further research is warranted to confirm these effects in larger cohorts and to explore long-term outcomes and individualized responses.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of University of Alicante (UA-2021-03-11).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to its inclusion of personal health information.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

ESR	Erythrocyte Sedimentation Rate
HbA1c	Glycated Hemoglobin
HDL	High-Density Lipoprotein
LDL	Low-Density Lipoprotein
MDA	Malondialdehyde
MPO	Myeloperoxidase
PCR	Polymerase Chain Reaction
RCT	Randomized Controlled Trial
ROS	Reactive Oxygen Species
SD	Standard Deviation
TG	Triglyceride

References

1. Nurkolis, F.; Kurniawan, R.; Kurniatanty, I.; Park, M.N.; Moon, M.; Fatimah, S.; Gunawan, W.B.; Surya, R.; Taslim, N.A.; Song, H.; et al. New Insight on In Vitro Biological Activities of Sulfated Polysaccharides from Ulvophyte Green Algae. *Molecules* **2023**, *28*, 4531. [CrossRef] [PubMed]
2. Ruan, Q.; Chen, Y.; Wen, J.; Qiu, Y.; Huang, Y.; Zhang, Y.; Farag, M.A.; Zhao, C. Regulatory Mechanisms of the Edible Alga *Ulva lactuca* Polysaccharide via Modulation of Gut Microbiota in Diabetic Mice. *Food Chem.* **2023**, *409*, 135287. [CrossRef] [PubMed]
3. Liang, Y.; Yu, W.; Wang, H.; Yao, L.; He, Z.; Sun, M.; Feng, T.; Yu, C.; Yue, H. Flash Extraction of Ulvan Polysaccharides from Marine Green Macroalga *Ulva linza* and Evaluation of Its Antioxidant and Gut Microbiota Modulation Activities. *Int. J. Biol. Macromol.* **2024**, *262*, 130174. [CrossRef] [PubMed]

4. Paiva, L.; Lima, E.; Neto, A.I.; Marcone, M.; Baptista, J. Nutritional and Functional Bioactivity Value of Selected Azorean Macroalgae: *Ulva compressa*, *Ulva rigida*, *Gelidium microdon*, and *Pterocladiella capillacea*. *J. Food Sci.* **2017**, *82*, 1757–1764. [CrossRef] [PubMed]
5. Puengpan, S.; Phetrungnapha, A.; Sattayakawee, S.; Tunsophon, S. Phycocyanin Attenuates Skeletal Muscle Damage and Fatigue via Modulation of Nrf2 and IRS-1/AKT/MTOR Pathway in Exercise-Induced Oxidative Stress in Rats. *PLoS ONE* **2024**, v*19*, e0310138. [CrossRef] [PubMed]
6. González, A.; Vidal, C.; Espinoza, D.; Moenne, A. Anthracene Induces Oxidative Stress and Activation of Antioxidant and Detoxification Enzymes in *Ulva lactuca* (Chlorophyta). *Sci. Rep.* **2021**, *11*, 7748. [CrossRef] [PubMed]
7. Clemente-Suárez, V.J.; Bustamante-Sanchez, Á.; Mielgo-Ayuso, J.; Martínez-Guardado, I.; Martín-Rodríguez, A.; Tornero-Aguilera, J.F. Antioxidants and Sports Performance. *Nutrients* **2023**, *15*, 2371. [CrossRef] [PubMed]
8. Mason, S.A.; Morrison, D.; McConell, G.K.; Wadley, G.D. Muscle Redox Signalling Pathways in Exercise. Role of Antioxidants. *Free Radic. Biol. Med.* **2016**, *98*, 29–45. [CrossRef] [PubMed]
9. Suzuki, K.; Tominaga, T.; Ruhee, R.T.; Ma, S. Characterization and Modulation of Systemic Inflammatory Response to Exhaustive Exercise in Relation to Oxidative Stress. *Antioxidants* **2020**, *9*, 401. [CrossRef] [PubMed]
10. Muniz-Santos, R.; Bassini, A.; Falcão, J.; Prado, E.; Martin, L.R.; Chandran, V.; Jurisica, I.; Cameron, L.C. Sportomics Analyses of the Exercise-Induced Impact on Amino Acid Metabolism and Acute-Phase Protein Kinetics in Female Olympic Athletes. *Nutrients* **2024**, *16*, 3538. [CrossRef] [PubMed]
11. Arzhang, P.; Arghavan, H.; Kazeminejad, S.; Mohammadi, F.; Baniasadi, M.M.; Bavani, N.G.; Darvishi, H.; Azadbakht, L. The Effect of Algae Supplementation on Lipid Profile and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Funct. Foods* **2024**, *122*, 106461. [CrossRef]
12. Wells, M.L.; Potin, P.; Craigie, J.S.; Raven, J.A.; Merchant, S.S.; Helliwell, K.E.; Smith, A.G.; Camire, M.E.; Brawley, S.H. Algae as Nutritional and Functional Food Sources: Revisiting Our Understanding. *J. Appl. Phycol.* **2017**, *29*, 949–982. [CrossRef] [PubMed]
13. Taboada, C.; Millán, R.; Míguez, I. Composition, Nutritional Aspects and Effect on Serum Parameters of Marine Algae *Ulva rigida*. *J. Sci. Food Agric.* **2010**, *90*, 445–449. [CrossRef] [PubMed]
14. Wang, C.; Min, R.; Zhou, Q.; Qi, Y.; Ma, Y.; Zhang, X. Multiple Health Outcomes Associated with Algae and Its Extracts Supplementation: An Umbrella Review of Systematic Reviews and Meta-Analyses. *Phytother. Res.* **2024**, *38*, 5162–5183. [CrossRef] [PubMed]
15. Ding, K.X.; Gao, T.L.; Xu, R.; Cai, J.; Zhang, H.Q.; Sun, Y.Y.; Zhong, F.; Ma, A.G. Quantifying the Effect of Supplementation with Algae and Its Extracts on Glycolipid Metabolism: A Meta-Analysis of Randomized Controlled Trials. *Nutrients* **2020**, *12*, 1712. [CrossRef] [PubMed]
16. Widianingsih, W.; Salamah, N.; Maulida, F.Q. The Effects of Ethanolic Extract of Green Algae (*Ulva lactuca* L.) on Blood Cholesterol Levels in Male Rats Induced by a High Fat Diet. *J. Kedokt. Dan Kesehat. Indones.* **2009**, *7*, 181–186. [CrossRef]
17. Chen, Y.; Ouyang, Y.; Chen, X.; Chen, R.; Ruan, Q.; Farag, M.A.; Chen, X.; Zhao, C. Hypoglycaemic and Anti-Ageing Activities of Green Alga *Ulva lactuca* Polysaccharide via Gut Microbiota in Ageing-Associated Diabetic Mice. *Int. J. Biol. Macromol.* **2022**, *212*, 97–110. [CrossRef] [PubMed]
18. Tong, A.; Wang, D.; Jia, N.; Zheng, Y.; Qiu, Y.; Chen, W.; El-Seed, H.R.; Zhao, C. Algal Active Ingredients and Their Involvement in Managing Diabetic Mellitus. *Biology* **2024**, *13*, 904. [CrossRef] [PubMed]