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HIIT and Aloe Vera Supplementation Improve METRNL Levels, Reduce Oxidative Stress, and Enhance Antioxidant Status in Men With Type 2 Diabetes

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ABSTRACT

Background: Hyperglycaemia, oxidative stress, and chronic inflammation play critical roles in the pathogenesis and progression of type 2 diabetes mellitus (T2DM). This study aimed to evaluate the effects of high-intensity interval training (HIIT), Aloe vera supplementation, and their combination on Meteorin-like (METRNL) protein levels, oxidative stress markers, and antioxidant status in men with T2DM.

Methods: In this semi-experimental study, 44 men with T2DM (aged 25–40 years) were randomly assigned to one of four groups (n = 11 per group): (1) HIIT, (2) Aloe vera supplementation, (3) HIIT + Aloe vera, and (4) Control. The HIIT protocol was conducted three times per week for 12 weeks. Participants in the Aloe vera groups received two 100 mg capsules of Aloe vera gel powder daily, one in the morning upon waking and one after dinner. Fasting blood samples were collected before and after the intervention. Data were analysed using two-way repeated-measures ANOVA, paired-sample *t*-tests, and Bonferroni post hoc comparisons.

Results: HIIT, Aloe vera supplementation, and their combination significantly increased METRNL, glutathione peroxidase (GPx), superoxide dismutase (SOD), and total antioxidant capacity (TAC), while significantly reducing malondialdehyde (MDA) levels compared with the control group ($p < 0.001$). The HIIT + Aloe vera group demonstrated the greatest improvements across all markers, followed by HIIT alone, while Aloe vera alone produced moderate but significant effects.

Conclusion: Both HIIT and Aloe vera supplementation independently improved antioxidant defence and reduced oxidative stress in men with T2DM, however, their combination elicited the most pronounced benefits, suggesting a synergistic effect. These findings support integrating structured exercise with phototherapeutic supplementation as a complementary strategy to enhance metabolic health in T2DM.

Keywords: anaerobic, metabolic inflammation, adipokines, complementary treatment

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) represents one of the most prevalent metabolic disorders worldwide, characterised by chronic hyperglycaemia, impaired insulin secretion, and peripheral insulin resistance (Vivarelli et al., 2013). Excess adiposity, which commonly coexists with T2DM, contributes to metabolic dysfunction by releasing pro-inflammatory cytokines (e.g. TNF-α, IL-6) and adipokines from adipose and hepatic tissues (American Diabetes Association Professional Practice Committee, 2022). These mediators amplify systemic inflammation, impair insulin signalling, and increase the risk of diabetic complications such as dyslipidaemia, endothelial dysfunction, and cardiovascular disease (Hu et al., 2014).

In recent years, circulating proteins – particularly myokines and adipokines – have gained attention as biomarkers and potential therapeutic targets for improving insulin sensitivity and managing T2DM (Hu et al., 2014). Among these, Meteorin-like protein (METRNL), a recently identified myokine/adipokine, has attracted attention due to its pleiotropic functions in energy expenditure, thermogenesis, glucose homeostasis, and immune modulation (Jung et al., 2018; Li et al., 2014; Zheng et al., 2016). METRNL expression increases in skeletal muscle following exercise and in adipose tissue during cold exposure, suggesting roles in both metabolic and inflammatory regulation. Clinical data indicate that individuals with T2DM exhibit reduced circulating METRNL concentrations, which negatively correlate with glucose levels and insulin resistance (Lee et al., 2018). These findings highlight METRNL as a promising biomarker and potential therapeutic target in diabetes management.

Another hallmark of T2DM is oxidative stress, driven by an imbalance between reactive oxygen species (ROS) generation and antioxidant defence mechanisms. Chronic hyperglycaemia induces mitochondrial overproduction of ROS, activates protein kinase C pathways, and increases the formation of advanced glycation end products, which collectively contribute to cellular injury and low-grade inflammation (Oguntibeju, 2019). Although the body's endogenous antioxidant systems, including enzymes like glutathione peroxidase and superoxide dismutase, respond to elevated oxidative stress, their capacity is often overwhelmed in diabetic patients (Park & Kwak, 2016). Thus, therapeutic interventions aimed at reducing ROS and enhancing antioxidant defences are considered vital for slowing disease progression.

Herbal medicines have emerged as promising adjuncts in diabetes management due to their combined anti-inflammatory and antioxidant properties (Dolinsky et al., 2013). Among these, Aloe vera (Aloe vera [L.] Burm.f., family Xanthorrhoeaceae), widely used across cultures, is rich in vitamins C and E, as well as phytochemicals such as barbaloin, isobarbaloin, and aloenin. These compounds have been shown to scavenge free radicals, protect pancreatic β-cells, and exert hypoglycaemic effects (Rajasekaran et al., 2006; Tabatabaei et al., 2017; Vivarelli et al., 2013). Experimental studies using diabetic animal models have confirmed Aloe vera's ability to lower blood glucose levels and modulate oxidative stress, further supporting its potential as a complementary therapeutic agent. Furthermore, Aloe vera has been reported to improve lipid profiles and upregulate endogenous antioxidant enzymes in diabetic animal models, reinforcing its role as a potential complementary therapeutic intervention (Misawa et al., 2008; Rajasekaran et al., 2004).

While there are many factors that contribute to the accumulation of excess body fat over time, inadequate physical exercise has received a lot of attention as a behaviour that can make people more likely to have a positive energy balance (Abbassi-Daloii, 2024; Zahabi, 2015; Zahabi et al., 2015; Zahabi, 2024). Physical activity, particularly high-intensity interval training (HIIT), is widely recognised as an effective non-pharmacological intervention for improving glycaemic control in individuals with T2DM. HIIT stimulates skeletal muscle glucose uptake by promoting GLUT4 translocation, enhances mitochondrial biogenesis, and improves whole-body insulin sensitivity. Importantly, HIIT has been shown to activate exercise-induced myokines, including METRNL, thereby linking muscle contraction to systemic metabolic adaptations (Hussey et al., 2012). Recent studies have also reported that short-term HIIT interventions can upregulate METRNL gene expression and improve redox balance by increasing antioxidant enzymes such as GPx and SOD, while reducing malondialdehyde, a marker of lipid peroxidation (Eaton et al., 2018; Gaeini & Ghardashi Afousi, 2017; Hooshmand et al., 2019; Jouybari et al., 2014). However, results are not entirely consistent; some studies have reported minimal or no changes in METRNL expression following aerobic training (Rao et al., 2014), highlighting the need for further research.

Given the overlapping mechanisms of Aloe vera and HIIT, both of which target oxidative stress, inflammation, and insulin resistance, their combined application may exert synergistic effects on metabolic regulation. Aloe vera supplementation could enhance the antioxidant and anti-inflammatory adaptations induced by HIIT, while exercise may potentiate Aloe vera's impact on circulating METRNL and redox homeostasis (Francois &

Little 2015; Jiménez-Maldonado et al., 2020; Rahimi et al., 2020).

Despite the potential relevance of this combined strategy, no human studies to date have investigated its effects on METRNL concentrations and oxidative–antioxidant biomarkers in T2DM populations.

Aim & hypothesis

Aim: To evaluate the effects of a 12-week high-intensity interval training (HIIT) programme, Aloe vera supplementation, and their combination on plasma Meteorin-like (METRNL) concentrations and oxidative–antioxidant status in men with type 2 diabetes mellitus (T2DM).

Hypothesis:

- **Null hypothesis (H_0):** There are no significant effects of HIIT, Aloe vera supplementation, or their combination on plasma METRNL concentrations, oxidative stress markers, or antioxidant status in men with T2DM.
- **Alternative hypothesis (H_1):** HIIT, Aloe vera supplementation, and especially their combination significantly improves plasma METRNL concentrations, enhances antioxidant enzyme activity, and reduces oxidative stress in men with T2DM.

2. METHODS

Research design

This semi-experimental study recruited participants through purposive sampling based on predefined eligibility criteria. Men aged 25–35 years diagnosed with type 2 diabetes mellitus (T2DM) were screened for inclusion. Recruitment was carried out through direct outreach and advertisements in Iran. Following screening, eligible participants were randomly allocated into four groups (n = 11 per group) using a systematic randomisation procedure to ensure balanced distribution across interventions (n = 11 per group).

Prior to enrolment, all participants provided written informed consent after receiving a detailed explanation of the study objectives, procedures, potential benefits, and risks. Participants were familiarised with various aspects, including training protocols, pre- and post-test measurements, and study timelines. Training sessions were performed on the same days for all intervention groups (Monday, Wednesday, and Friday or Saturday) under the supervision of at least two experienced trainers. Baseline and post-intervention measurements were conducted for all groups before and after the 12-week programme. Participation was entirely voluntary, and subjects were informed of their right to withdraw from the study at any time without penalty. Participants deemed medically unfit for high-intensity exercise, based on a screening electrocardiogram evaluated by a cardiologist, were excluded. Throughout the study, participants were regularly monitored; if the principal investigator or supervising physician identified any health risks, the participant was withdrawn for safety reasons.

Intervention protocols:

The study protocol consisted of the following components:

I. *High-intensity interval training (HIIT) group*: Sessions were conducted three times per week for 12 weeks. Bicycle ergometer resistance was initially set to minimal load to allow smooth transitions and to maintain target intensity. The HIIT programme followed the protocol of Trapp et al. (2008), consisting of 8 seconds of fast pedalling (~80% HRmax) followed by 12 seconds of slow pedalling (20–30 rpm), repeated for up to 60 cycles per 20-minute session. After each session, participants performed a 5-minute active recovery period at low resistance.

II. *Aloe vera supplementation group*: Participants received Aloe vera capsules containing 100 mg of Aloe vera gel powder, taken twice daily (Hęś et al., 2019), once before breakfast and once after dinner with 250 mL of water. Capsules were prepared, standardised, and coded by pharmaceutical staff from the University's Medical faculty, who were not otherwise involved in the trial.

III. *HIIT + aloe vera group*: Participants underwent a combined intervention consisting of the HIIT programme and Aloe vera supplementation for 12 weeks.

IV. *Control group*: Participants were instructed to maintain their habitual lifestyle and refrain from initiating any new structured exercise or supplementation programme during the study period.

Sampling method and sample size calculation

The sample size (n = 11 per group) was determined based on feasibility considerations and consistency with studies examining exercise and supplementation studies in T2DM populations. Participants were recruited using purposive sampling to ensure that all met predefined eligibility criteria, followed by systematic randomisation to ensure balanced allocation.

Inclusion criteria specified males with T2DM and aged between 25 and 30 years with a body mass index within the range of 25–30 kg/m². Recruitment occurred in Iran through direct outreach and advertising. Participants were eligible if they met all of the following:

1. Male adults diagnosed with T2DM at least three months prior to enrolment, according to standard clinical criteria.
2. Physically inactive, as defined by the International Physical Activity Questionnaire (Maddison et al., 2007).
3. Under stable medical treatment for T2DM (excluding insulin therapy).
4. Free from musculoskeletal injuries or chronic health conditions that would prevent safe participation in high-intensity exercise.
5. Following a balanced diabetic diet, assessed via a Food Frequency Questionnaire (Amsah et al., 2023), including low-glycaemic foods rich in fibre, protein, and healthy fats.

Exclusion criteria included allergies to Aloe vera, chronic illnesses, or certain medications. Participants were also excluded if they had:

1. Fasting blood glucose >270 mg/dL.
2. Use of exogenous insulin.
3. Severe diabetic complications (advanced proliferative retinopathy, overt nephropathy, diabetic ketoacidosis, severe neuropathy).
4. Hereditary glucose or galactose malabsorption.

Monitoring and compliance

Participants were instructed to maintain their habitual diet and daily activity levels throughout the intervention. Dietary intake was monitored using 3-day food records, and physical activity was tracked with weekly self-reported logs. Adherence to HIIT sessions and Aloe vera supplementation was monitored via attendance records and capsule counts. Randomisation was conducted using computer generation, and outcome assessors were blinded to group allocation to minimise bias.

A total of 49 men with T2DM were screened. Five withdrew prior to baseline testing, leaving 44 participants who completed the study. Group assignments included: (1) High-intensity interval training (HIIT), (2) Aloe vera supplementation, (3) HIIT + Aloe vera supplementation, and (4) Control. Participant demographics are summarised in Table 1.

Table 1. **Mean and standard deviation of the physical features of type 2 diabetic men according to the studied groups**

Variable	HIIT	Aloe vera supplementation	HIIT + Aloe vera supplementation	CG
Age (years)	27 ± 03	26 ± 05	28 ± 06	27 ± 04
Height (cm)	176.3 ± 4.6	178.1 ± 6.08	175.9 ± 5.31	174.1 ± 4.75
Weight (kg)	86.3 ± 4.21	84.1 ± 2.51	85.4 ± 3.46	85.9 ± 3.40
BMI (kg/m²)	27.8 ± 2.20	26.5 ± 1.94	27.9 ± 1.96	28.4 ± 2.56

Note: BMI – body mass index; CG – control group; HIIT – high-intensity interval group.

Experimental measurements and procedure of data collection

This study employed a randomised, single-blind, controlled trial design. Biochemical parameters were assessed at two time points: baseline (pre-intervention) and 12 weeks post-intervention. All biochemical analyses were conducted in a certified laboratory. Testing sessions were scheduled between 8:00 AM and 10:00 AM, and all blood samples were collected in a fasting state before breakfast.

Before beginning the experimental protocol, each participant completed four pre-intervention laboratory visits:

- Visit 1: ECG stress test, administered and interpreted by a cardiologist to assess cardiovascular suitability for exercise.
- Visit 2: Blood sample collection for biochemical analysis, conducted after a minimum 72-hour rest period.
- Visit 3: Participants performed a maximal incremental exercise test on a calibrated

cycle ergometer Monark 894E (*Monark Exercise AB, Vansbro, Sweden*) to determine individual maximal heart rate (HRmax), which was used to prescribe HIIT intensity. The Monark 894E is a mechanically braked cycle ergometer, calibrated prior to testing according to the manufacturer's specifications. Heart rate was continuously monitored using the Polar Team System H7 (*Polar Electro Oy, Kempele, Finland*), which provides real-time HR data and stores measurements for subsequent analysis. Participants also completed a familiarisation session during this visit to ensure proper use of the equipment and protocol adherence.

Blood collection and biochemical analysis

Fasting venous blood samples were collected from the right antecubital vein 72 hours before and after the 12-week intervention to avoid acute effects of exercise. All collections were performed between 8:00 AM and 10:00 AM under standardised laboratory conditions. Participants were instructed to abstain from caffeine, alcohol, and strenuous physical activity for at least 24 hours prior to sampling. Samples were drawn into EDTA-treated tubes and immediately placed on ice. Within 30 minutes, tubes were centrifuged at 3,000 rpm for 10 minutes at 4°C. The separated plasma was aliquoted into sterile microtubes and stored at −70°C until biochemical analyses were conducted.

Plasma METRNL concentrations were quantified using a commercial ELISA kit (*MyBioSource, San Diego, CA, USA*) with a sensitivity of <0.64 ng/mL and a detection range of 1.56–100 ng/mL. Plasma antioxidant enzymes and oxidative stress markers, including glutathione peroxidase (GPx), superoxide dismutase (SOD), total antioxidant capacity (TAC), and malondialdehyde (MDA), were measured using ELISA kits from Abcam (*Cambridge, MA, USA*), following the manufacturers' protocols.

All biochemical assays were performed in duplicate using a SpectraMax iD3 Multi-Mode Microplate Reader (*Molecular Devices, San Jose, CA, USA*). For quality assurance, the intra-assay and inter-assay coefficients of variation (CVs) were maintained below 10% and 12%, respectively, consistent with the manufacturers' specifications.

Statistical analysis

Data were analysed using IBM SPSS Statistics version 25.0 Software (*IBM Corp., Chicago, IL, USA*). All data are presented as mean ± standard deviation (SD). Normality of distribution was assessed using the Shapiro–Wilk test, and homogeneity of variances was confirmed using Levene's test. Within-group (pre- vs. post-intervention) comparisons were analysed using paired-sample *t*-tests, while two-way repeated-measures ANOVA was applied to evaluate group × time interactions. When significant effects were observed, Tukey's post hoc test was used for pairwise comparisons. Statistical significance was set at $p < 0.05$.

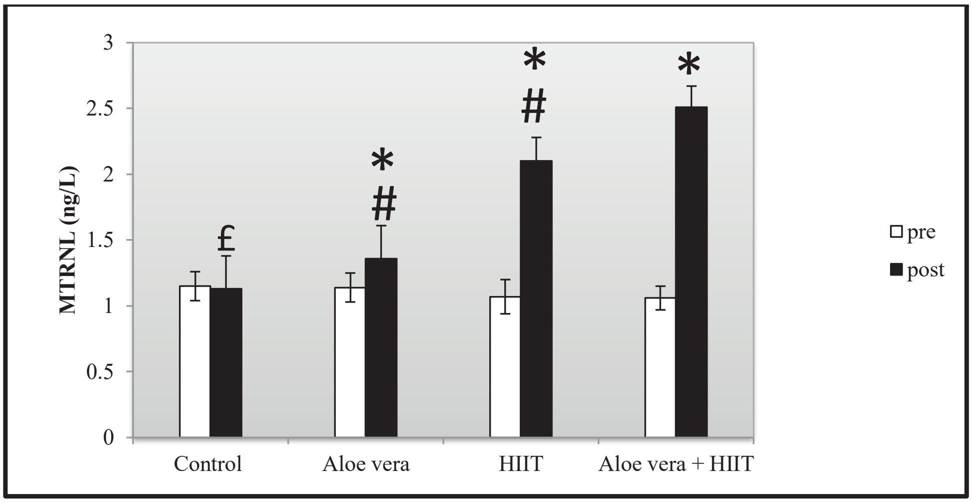
3. RESULTS

All variables were normally distributed (Shapiro–Wilk test), and homogeneity of variances was confirmed (Levene's test). Two-way repeated-measures ANOVA revealed significant group × time interactions for several biochemical parameters, as illustrated in the corresponding figures.

METRNL

A two-way repeated-measures ANOVA indicated a significant time × group interaction for METRNL levels ($F(3, 40) = 62.7$, $p < 0.001$, $\eta^2 = 0.856$), as well as a significant main effect of time ($F(1, 40) = 238.2$, $p < 0.001$, $\eta^2 = 0.825$). These findings indicate that changes in METRNL levels over time differed significantly among the groups (HIIT, Aloe vera, HIIT + Aloe vera, and Control), and that METRNL levels increased overall following the intervention. Bonferroni-adjusted post hoc comparisons revealed significant pre- to post-intervention increases in METRNL levels in all experimental groups compared to the Control group. Furthermore, the HIIT + Aloe vera group exhibited a significantly greater increase in METRNL compared to the HIIT group alone ($p = 0.023$). Paired-sample *t*-tests confirmed statistically significant pre-post improvements within each experimental group (Figure 1).

Figure 1. **Mean ± standard deviation of subjects' METRNL measures before and after the intervention period**

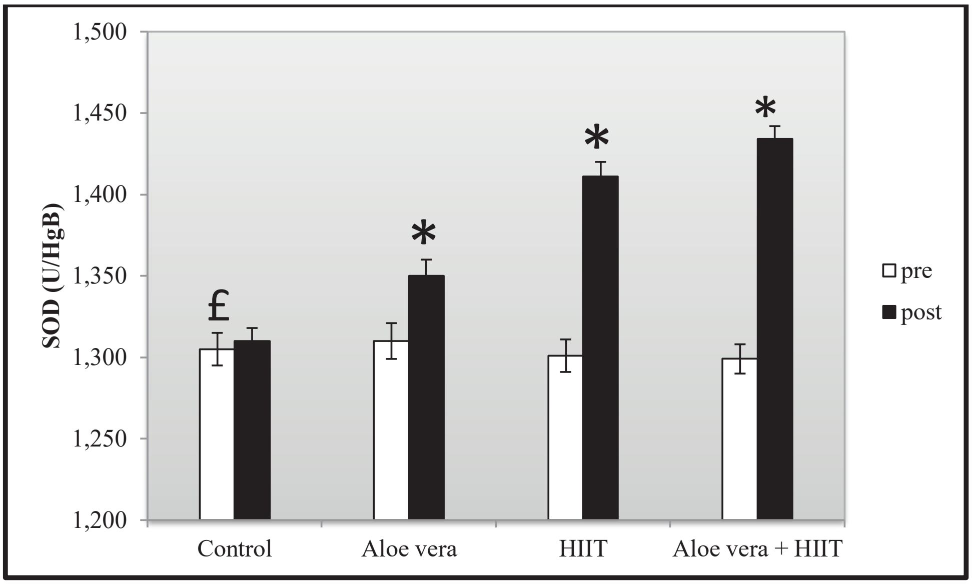


Notes: Control: control group; Aloe vera group: Aloe vera; training group: HIIT; Aloe vera training group: Aloe vera + HIIT. * – significant difference between pre- and post-test; £ – significant difference in Control compared to the HIIT and Aloe vera + HIIT; # – significant difference in Aloe vera compared to the HIIT and Aloe vera + HIIT and significant difference in HIIT compared to the Aloe vera + HIIT.

SOD

A two-way repeated-measures ANOVA revealed a significant time × group interaction for SOD levels ($F(3, 40) = 5.7$, $p = 0.002$, $\eta^2 = 0.430$), along with a significant main effect of time ($F(1, 40) = 33.0$, $p < 0.001$, $\eta^2 = 0.452$). These findings indicate that changes in SOD levels over time varied across the groups and that SOD levels significantly increased overall from pre- to post-intervention. Bonferroni-adjusted post hoc comparisons demonstrated significantly greater increases in SOD levels in both the HIIT group ($p = 0.015$) and the HIIT + Aloe vera group ($p = 0.002$) when compared to the Control group. Additionally, paired sample *t*-tests confirmed statistically significant pre- to post-intervention increases in SOD levels within each group (Figure 2).

Figure 2. **Mean ± standard deviation of subjects' SOD measures before and after the intervention period**

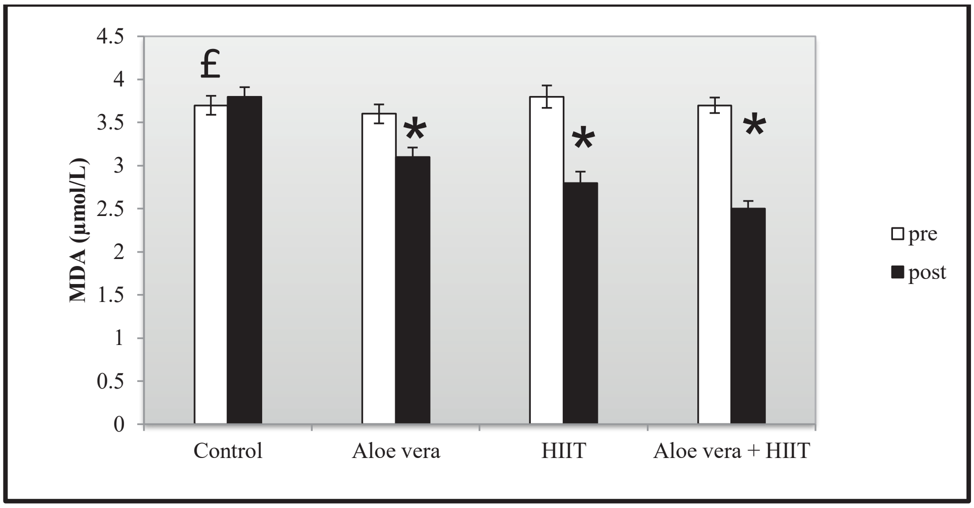


Notes: Control: control group; Aloe vera group: Aloe vera; training group: HIIT; Aloe vera training group: Aloe vera + HIIT. * – significant difference between pre- and post-test; £ – significant difference in Control compared to the HIIT and Aloe vera + HIIT.

MDA

A two-way repeated-measures ANOVA revealed a significant time × group interaction for MDA levels ($F(3, 40) = 14.39$, $p < 0.001$, $\eta^2 = 0.519$), as well as a significant main effect of time ($F(1, 40) = 75.73$, $p < 0.001$, $\eta^2 = 0.654$). These results indicate that MDA levels significantly changed over time, with the magnitude of change differing across groups. Bonferroni post hoc comparisons revealed significantly greater reductions in MDA levels in the HIIT group ($p = 0.014$), Aloe vera supplementation group ($p = 0.026$), and HIIT + Aloe vera group ($p = 0.001$) compared to the Control group. Paired sample *t*-tests also showed significant pre- to post-intervention decreases in MDA levels within all three experimental groups ($p < 0.001$ for each). These results are illustrated in Figure 3.

Figure 3. **Mean ± standard deviation of subjects' MDA measures before and after the intervention period**

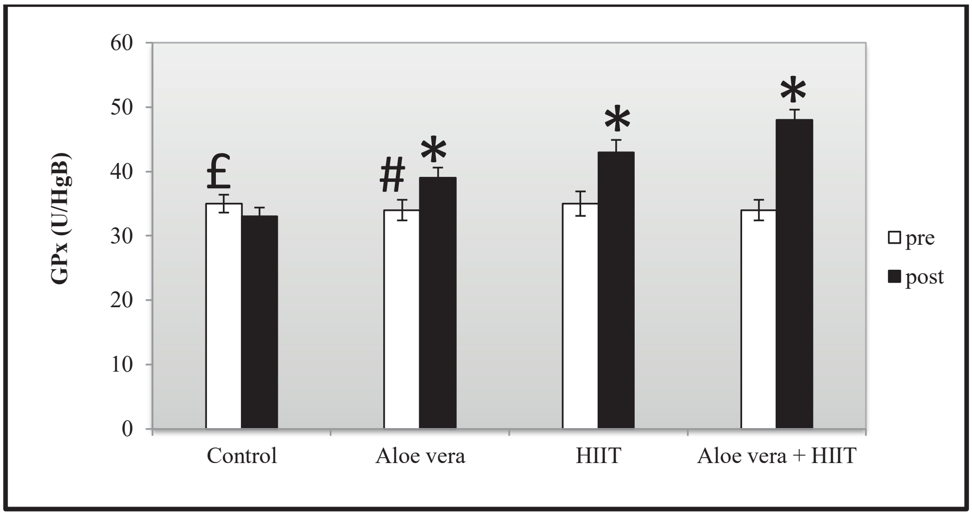


Notes: Control: control group; Aloe vera group: Aloe vera; training group: HIIT; Aloe vera training group: Aloe vera + HIIT. * – significant difference between pre- and post-test; £ – significant difference in Control compared to the Aloe vera, HIIT, and Aloe vera + HIIT.

GPx

A two-way repeated-measures ANOVA demonstrated a significant main effect of time on GPx levels, regardless of group assignment ($F(1, 40) = 46.2$, $p < 0.001$, $\eta^2 = 0.536$), indicating an overall increase from baseline to post-intervention. Additionally, a significant time × group interaction was observed ($F(3, 40) = 12.4$, $p < 0.001$, $\eta^2 = 0.482$), suggesting that changes in GPx levels varied across the intervention groups. Bonferroni-adjusted post hoc analysis revealed significant differences between the Control group and both the HIIT group ($p = 0.014$) and the HIIT + Aloe vera group ($p < 0.001$). Furthermore, the Aloe vera group differed significantly from the HIIT group ($p = 0.005$). Within-group comparisons using paired-sample *t*-tests indicated a significant increase in GPx levels from pre- to post-intervention in all three experimental groups ($p < 0.001$). These findings are presented in Figure 4.

Figure 4. **Mean ± standard deviation of subjects' GPx measures before and after the intervention period**

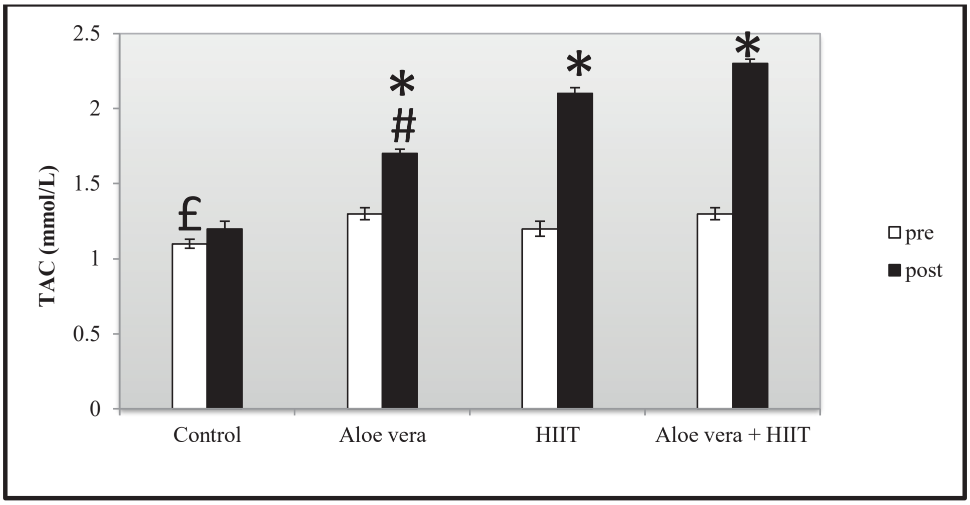


Notes: Control: control group; Aloe vera group: Aloe vera; training group: HIIT; Aloe vera training group: Aloe vera + HIIT. * – significant difference between pre- and post-test; £ – significant difference in Control compared to the HIIT and Aloe vera + HIIT; # – significant difference in Aloe vera compared to the Aloe vera + HIIT.

TAC

A two-way repeated-measures ANOVA revealed a significant main effect of time on total antioxidant capacity (TAC) levels across all groups ($F(1, 40) = 181.8$, $p < 0.001$, $\eta^2 = 0.820$), indicating a significant increase from baseline to post-intervention. Moreover, there was a significant time × group interaction ($F(3, 40) = 22.8$, $p < 0.001$, $\eta^2 = 0.631$), demonstrating that TAC changes over time differed among the intervention groups. Bonferroni-adjusted post hoc analyses showed significant differences between the Control group and each of the Aloe vera supplementation group ($p < 0.001$), HIIT group ($p < 0.001$), and HIIT + Aloe vera group ($p < 0.001$). Additionally, the Aloe vera group differed significantly from both the HIIT + Aloe vera group ($p < 0.001$) and the HIIT group ($p = 0.034$). Paired-sample *t*-tests revealed significant increases in TAC from pre- to post-intervention in the Aloe vera group ($p < 0.0001$), HIIT group ($p < 0.0001$), and HIIT + Aloe vera group ($p < 0.0001$), whereas the Control group showed a non-significant decrease ($p = 0.16$) (Figure 5).

Figure 5. **Mean ± standard deviation of subjects' TAC measures before and after the intervention period**



Notes: Control: control group; Aloe vera group: Aloe vera; training group: HIIT; Aloe vera training group: Aloe vera + HIIT. * – significant difference between pre- and post-test; £ – significant difference in Control compared to the HIIT, Aloe vera, and Aloe vera + HIIT; # – significant difference in Aloe vera compared to the HIIT and Aloe vera + HIIT.

4. DISCUSSION

The observed increase in METRNL after HIIT concurs with previous studies (Bae et al., 2018; Trapp et al., 2008; Zhang et al., 2016), supporting the notion that exercise can positively modulate this novel adipokine. METRNL is primarily expressed in white adipose tissue and skeletal muscle, where it regulates energy metabolism and insulin sensitivity. Its regulation is closely linked to the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), a central modulator of mitochondrial biogenesis and metabolism. Exercise induces PGC-1α expression, which in turn may stimulate METRNL production (Bae et al., 2018). Animal models deficient in PGC-1α show worsened insulin resistance under high-fat diet conditions, while overexpression of METRNL protects against these effects by improving glucose uptake and insulin signalling pathways (Pagel-Langenickel et al., 2008; Zheng et al., 2016). Thus, the increase in METRNL observed in our study may reflect enhanced PGC-1α activity triggered by HIIT; however, PGC-1α levels and insulin resistance parameters were not measured in the present study, representing a limitation and making interpretations speculative (Dong et al., 2024; Rao et al., 2014).

Additionally, METRNL has neurotrophic effects and promotes the 'browning' of white adipose tissue, a process that enhances energy expenditure and insulin sensitivity (Dong et al., 2024; Rao et al., 2014). Through these mechanisms, elevated METRNL levels may contribute to reduced insulin resistance and improved metabolic health in diabetic individuals. Differences between our findings and earlier studies reporting no METRNL change after aerobic exercise (Rao et al., 2014) may result from differences in exercise type, duration, and species-specific responses. The longer-term HIIT protocol used in our human participants likely provided a stronger metabolic stimulus than the short-term aerobic interventions used in animal models.

Oxidative stress plays a central role in the development and progression of T2DM by damaging cellular components and exacerbating insulin resistance. The balance between reactive oxygen species production and antioxidant defences is therefore critical (Bhatti et al., 2022; Henriksen et al., 2011). The significant increases in GPx, SOD, and TAC and the decrease in MDA observed in this study align with previous findings (Eaton et al., 2018), confirming that structured exercise enhances endogenous antioxidant capacity (Abbassi-Daloii et al., 2024). GPx and SOD neutralise superoxide radicals and hydrogen peroxide, preventing harmful chain reactions that lead to lipid peroxidation and cellular damage (Lobo et al., 2010). MDA serves as a reliable marker of lipid peroxidation; its reduction indicates decreased oxidative damage to membranes. Although this study did not include a healthy control group, previous evidence suggests similar adaptive antioxidant responses occur in both diabetic and non-diabetic individuals following HIIT and antioxidant supplementation (Pagel-Langenickel et al., 2008).

HIIT specifically induces transient oxidative stress by increasing oxygen consumption during exercise (Duansak et al., 2003). This acute stress serves as a signal to upregulate antioxidant defence systems adaptively, a phenomenon known as hormesis. Over time, repeated HIIT sessions strengthen antioxidant responses, lowering basal oxidative stress and protecting tissues from ROS-mediated injury. Aloe vera supplementation likely amplified these effects due to its bioactive components such as anthraquinones, chromones, flavonoids, and vitamins C and E, which possess potent antioxidant and anti-inflammatory properties (Hamman, 2008; Hęś, 2019; Saini & Saini, 2011).

These compounds scavenge free radicals, stabilise membranes, and reduce lipid peroxidation, as indicated by the decrease in MDA (Hęś, 2019). Aloe vera also facilitates the regeneration of reduced glutathione, a critical intracellular antioxidant that detoxifies ROS and protects pancreatic β-cells from oxidative injury (Radha & Laxmipriya, 2014).

Furthermore, Aloe vera has been reported to improve insulin secretion and glycaemic control in diabetic animal models, potentially through antioxidant-mediated preservation of β-cell function (Abo-Youssef & Messiha, 2013; Ramachandraiahgari et al., 2012). Its polysaccharides exhibit radical scavenging activity, and total phenolics from Aloe vera extracts significantly inhibit oxidative stress pathways (El-Shemy et al., 2010; Kumar et al., 2019). The combined intervention group showed the most pronounced improvements in all measured biomarkers, suggesting that exercise and Aloe vera act through complementary mechanisms. While HIIT enhances mitochondrial function and endogenous antioxidant defences, Aloe vera contributes exogenous antioxidants and anti-inflammatory molecules, jointly supporting redox balance and metabolic health.

This study has several limitations. The absence of direct assessments of PGC-1α and insulin resistance parameters restricts the mechanistic interpretation of METRNL regulation. Additionally, the lack of a healthy control group limits direct comparison. Future research should include molecular analyses, non-diabetic cohorts, and dose–response investigations of Aloe vera supplementation. Long-term, large-scale studies are warranted to validate these findings and explore their clinical implications for T2DM management.

5. CONCLUSIONS

In summary, this study demonstrated that high-intensity interval training (HIIT) combined with Aloe vera supplementation significantly increased circulating METRNL levels, enhanced antioxidant enzyme activity, elevated total antioxidant capacity, and reduced oxidative stress, as evidenced by decreased MDA concentrations in men with type 2 diabetes. Notably, the combined intervention produced superior effects compared to either treatment alone, suggesting a synergistic interaction between exercise-induced and phytochemical antioxidant mechanisms. These findings highlight the potential of integrating structured exercise programmes with phototherapeutic supplementation as an effective, non-pharmacological strategy to improve metabolic health and redox balance in individuals with type 2 diabetes. Future research should examine the long-term sustainability, optimal dosage, and molecular pathways underlying this combined approach to better establish its clinical relevance in diabetes management.

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Informed Consent Statement: A prior written consent was taken from all the participants who were willing to participate in the study and after that recruitment was done for the study.

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

Ethical Statement: This study was approved by the Ethics Committee of the Islamic Azad University (Ref. IR.IAU.M.REC.139), and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Additionally, the trial was registered with ClinicalTrials.gov (Identifier: NCT06377657).

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