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Astaxanthin Supplementation and Antioxidant Modulation in Methamphetamine Dependence: A Potential SIRT1/PGC-1α Pathway Mechanism.

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ABSTRACT:

Background: Methamphetamine (METH) addiction remains a significant global health challenge, characterized by profound neurotoxicity and cognitive impairment. Emerging evidence suggests that the pathophysiology of METH dependence is closely linked to oxidative stress, where an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms leads to neuronal damage.

Aim: to evaluate the impact of Astaxanthin supplementation on antioxidant levels in methamphetamine-dependent patients, while investigating the mediating role of the SIRT1/PGC-1α pathway.

Method: A total of ninety men, aged between 18 and 45 years, The study design is as follows Group 1: Healthy individuals, non-drug users (control group),Group 2: Drug users who had been using methamphetamine for one year and Group 3: Drug users who had been using methamphetamine for one year and were administered astaxanthin treatment at a dose of 12 mg/day for thirty days.

Result: methamphetamine exposure induced significant oxidative damage and suppressed key neuroprotective markers. Specifically, MDA levels were markedly elevated in the untreated group (5.97 \pm 1.98) compared to controls (2.07 \pm 0.60), while Astaxanthin treatment significantly reduced these levels to 4.38 \pm 1.28 ($p < 0.001$). Similarly, the compensatory increase in Catalase activity observed in the untreated group (56.07 \pm 16.24) was partially normalized following treatment (46.00 \pm 13.48). At the molecular level, methamphetamine exposure caused a substantial decline in PGC-1α and SIRT1 levels; however, Astaxanthin supplementation facilitated a significant partial recovery of both biomarkers (0.76 \pm 0.40 and 0.81 \pm 0.46, respectively). Overall, these findings demonstrate that Astaxanthin effectively mitigates oxidative stress and modulates the SIRT1/PGC-1α pathway, although levels did not return to baseline control values.

Conclusion: Astaxanthin (AST) acts as a potent neuroprotective agent in the context of methamphetamine (METH) dependence by modulating the SIRT1/PGC-1α signaling pathway.

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INTRODUCTION

The relationship between substance use and mental health is complex [1], and both constitute a substantial global public health burden [2]. In 2018, it was estimated that the annual financial costs of alcohol-related harm and illicit drug use in the UK were GBP 21.5 billion and GBP 10.7 billion, respectively [3,4], and according to the Mental Health Foundation in 2022, mental health problems cost the UK economy at least GBP 117.9 billion annually [5]. Mental health disorders and problematic substance use are more common in socioeconomically deprived areas [6], and the North East of England has the second-highest low income and deprivation rates in England after inner London [7], with high levels of mental health, substance, and alcohol use problems compared to the rest of the country [8,9]. Comparison across all twelve local authorities in North East England revealed that all but one had higher-than-national-average rates of deaths from drug misuse, with the average rate across the region at 9.9 per 100,000 in 2018–2020, compared to 3.5 per 100,000 in the lowest region (London) [10]. The region has a high admission rate to hospitals for mental and

behavioural disorders due to alcohol (108.8/100,000 population compared with 72.3/100,000 for England), and whilst the suicide rate in the region has remained relatively static in recent years, premature mortality from all causes for people with a mental illness remains extremely high in all local authority areas [8].

Toxicities from methamphetamine use are dominated by vascular and neuropsychiatric pathologies; clinical management to-date has been markedly limited. Like most psychoactive substances, methamphetamine can affect multiple organ systems, from neurologic to renal, and many of these toxicities are associated with route of administration. However, in contrast to opioids, which generally result in acute toxicity and death through suppression of the respiratory drive.

Methodology and Study Design

Participant Profile and Ethical Compliance

This clinical investigation involved 90 male subjects (age range: 18–45 years). The cohort was sourced from the Social Rehabilitation Center's specialized drug treatment units. Ethical oversight was maintained in strict accordance with the "Task Facilitation Manual" of the College of Pharmacy, Al-Mustansiriya University, with formal clinical approval granted by the Medical City Teaching Hospital.

Experimental Groups

The participants were equally allocated into three distinct cohorts (n=30 per group) to evaluate the therapeutic efficacy of Astaxanthin over a 30-day period:

• **Control Group (Group 1):** Comprised of healthy, non-drug-using volunteers.

• **Methamphetamine Group (Group 2):** Included individuals with a documented one-year history of methamphetamine use.

• **Intervention Group (Group 3):** Included methamphetamine users (one-year duration) who received a daily oral dose of 12 mg of Astaxanthin for one month prior to biochemical assessment.

Biomarker Analysis and Molecular Assessment

To investigate the mechanisms of neuroprotection and mitochondrial modulation, the following parameters were evaluated:

1. Oxidative Stress Profiling

A comprehensive biochemical analysis was conducted to quantify markers of oxidative damage and antioxidant status, specifically:

• Malondialdehyde (MDA)

• Superoxide Dismutase (SOD)

• Glutathione (GSH)

• Catalase

2. Genetic Expression Analysis

A molecular approach was employed to determine the mRNA expression levels of SIRT1 and PGC-1α. This was performed on homogenized liver tissue samples utilizing Real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) to assess changes at the genomic level.

RESULTS

Oxidative Stress and Antioxidant Biomarkers Across Study Groups

In table 1, the analysis revealed a significant reduction in SOD levels in the Meth (untreated) group (2.83 ± 1.01) compared to the Control group (4.76 ± 0.85), indicating impaired antioxidant defense following methamphetamine exposure. The treated group demonstrated a partial recovery (3.94 ± 1.29), being significantly higher than the untreated group but still below the control level ($F = 24.73$, $p < 0.001$). The observed pattern (a > b > c) suggests that astaxanthin contributes to restoring enzymatic antioxidant activity, although full normalization was not achieved.

GSH levels were significantly decreased in the untreated group (3.76 ± 1.26) compared to the control group (6.81 ± 1.53), reflecting depletion of non-enzymatic antioxidant reserves. In contrast, the treated group (6.27 ± 1.55) showed values statistically comparable to the control group (a = a > c), indicating near-complete restoration of glutathione levels following astaxanthin administration ($F = 37.60$, $p < 0.001$). This pattern points to a strong recovery of intracellular redox balance.

MDA levels, representing lipid peroxidation, were markedly elevated in the untreated group (5.97 ± 1.98) compared to the control group (2.07 ± 0.60), confirming increased oxidative damage. Treatment significantly reduced MDA levels (4.38 ± 1.28), although they remained higher than control values ($F = 58.44$, $p < 0.001$). The pattern (a > b > c) reflects a clear attenuation of oxidative stress following treatment, yet without complete normalization.

Catalase activity was significantly increased in the untreated group (56.07 ± 16.24) compared to the control group (37.13 ± 9.75), likely representing a compensatory response to excessive oxidative stress. The treated group exhibited intermediate values (46.00 ± 13.48), significantly lower than the untreated group but still higher than control ($F = 14.94$, $p < 0.001$). This gradient (a > b > c) suggests partial normalization of enzymatic antioxidant defenses after astaxanthin treatment.

Table 1. Comparison of Oxidative Stress Markers Across Study Groups

Parameter	Control	Meth (Untreated)	Meth + Astaxanthin	F-value	p-value
SOD (U/mL)	**4.76 ± 0.85[a]**	**2.83 ± 1.01[c]**	**3.94 ± 1.29[b]**	**24.73**	**<0.001***
GSH (µmol/L)	**6.81 ± 1.53[a]**	**3.76 ± 1.26[c]**	**6.27 ± 1.55[a]**	**37.60**	**<0.001***
MDA (nmol/mL)	**2.07 ± 0.60[c]**	**5.97 ± 1.98[a]**	**4.38 ± 1.28[b]**	**58.44**	**<0.001***

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Parameter	Control	Meth (Untreated)	Meth + Astaxanthin	F-value	p-value
Catalase (U/mL)	37.13 ± 9.75[c]	56.07 ± 16.24[a]	46.00 ± 13.48[b]	14.94	<0.001*

* Significant at $p < 0.05$
Different letters indicate significant differences (LSD test).

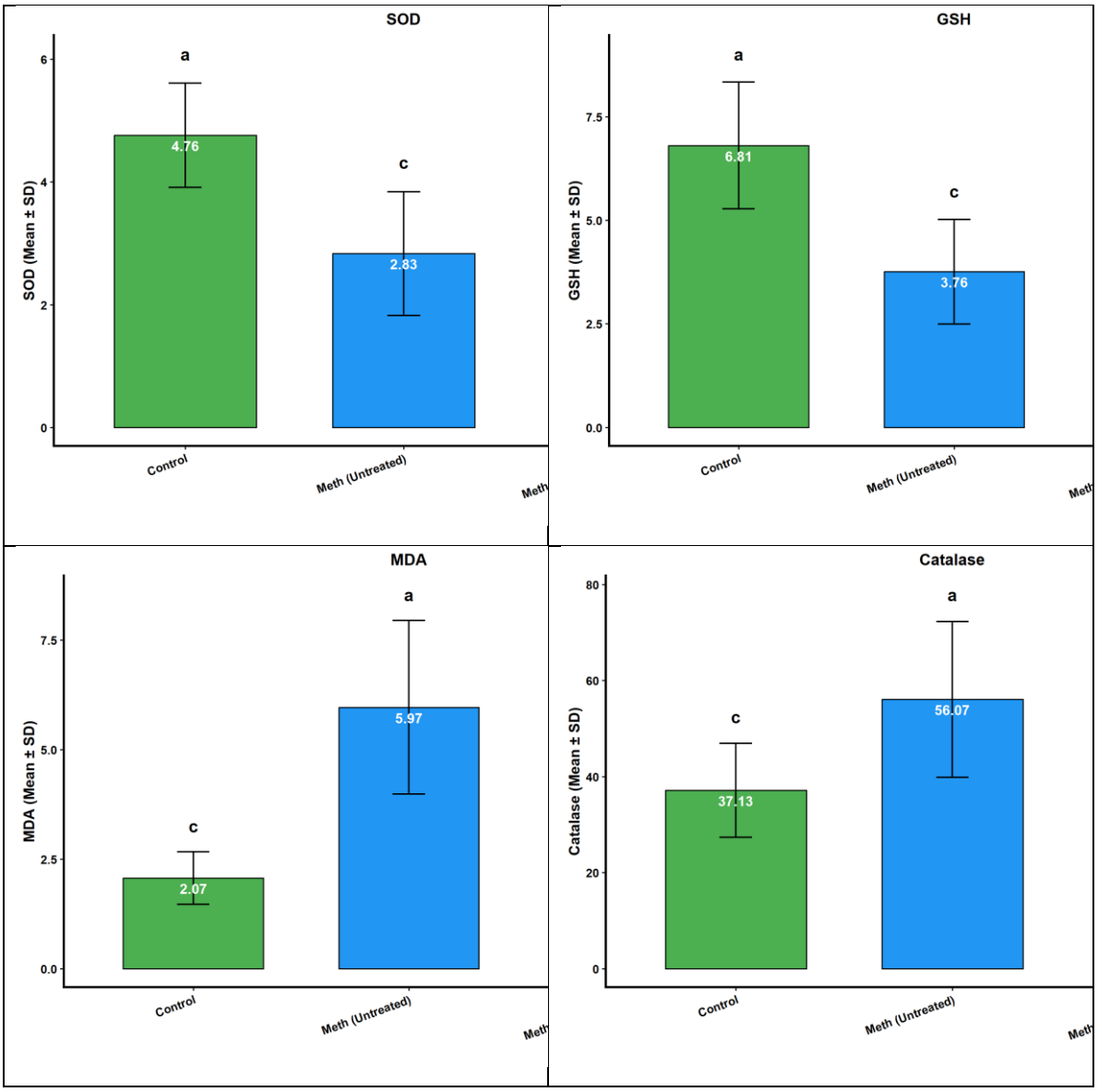

Figure 1. Comparison of Oxidative Stress Markers Across Study Groups

Effect of Methamphetamine Exposure and Treatment on PGC1 and SIRT1 Levels

This section examines the impact of methamphetamine exposure and subsequent treatment on key metabolic regulators, PGC1 and SIRT1, which are closely linked to mitochondrial function and cellular energy homeostasis. By comparing healthy

controls with methamphetamine users before and after treatment, the analysis aims to determine whether therapeutic intervention can restore biomarker levels toward normal physiological ranges.

Table (1) shows a clear reduction in both PGC1 and SIRT1 levels in the Meth-Pre group compared to the Control group. Specifically, PGC1 decreased from **1.28 ± 0.54** in controls to **0.39 ± 0.24** before treatment, while SIRT1 dropped from **1.30 ± 0.60** to **0.41 ± 0.22**, indicating substantial suppression of these biomarkers with methamphetamine exposure. Following treatment, partial recovery was observed, with PGC1 increasing to **0.76 ± 0.40** and SIRT1 to **0.81 ± 0.46**. However, both markers remained below control levels, suggesting incomplete restoration. The relatively wider standard deviations in the control and post-treatment groups indicate moderate variability in biomarker expression.

Table (1). Descriptive Statistics of PGC1 and SIRT1 According to Study Groups

Variable	Group	N	Mean ± SD	Std. Error	95% CI (Lower–Upper)	Min	Max
PGC1	**Control**	**30**	**1.28 ± 0.54**	**0.10**	**1.08 – 1.48**	**0.0019**	**2.53**
	Meth-Pre	**30**	**0.39 ± 0.24**	**0.04**	**0.30 – 0.48**	**0.10**	**0.96**
	Meth-Post	**30**	**0.76 ± 0.40**	**0.07**	**0.61 – 0.91**	**0.27**	**1.79**
	Total	**90**	**0.81 ± 0.55**	**0.06**	**0.69 – 0.92**	**0.0019**	**2.53**
SIRT1	**Control**	**30**	**1.30 ± 0.60**	**0.11**	**1.08 – 1.53**	**0.0013**	**3.15**
	Meth-Pre	**30**	**0.41 ± 0.22**	**0.04**	**0.33 – 0.49**	**0.11**	**1.04**
	Meth-Post	**30**	**0.81 ± 0.46**	**0.08**	**0.64 – 0.98**	**0.20**	**2.74**
	Total	**90**	**0.84 ± 0.58**	**0.06**	**0.72 – 0.96**	**0.0013**	**3.15**

The ANOVA results in Table (2) demonstrate statistically significant differences among the three groups for both biomarkers. For PGC1, the between-group variance was significant (**F = 35.03, p < 0.001**), while SIRT1 also showed a strong group effect (**F = 28.86, p < 0.001**). These findings confirm that methamphetamine exposure and treatment status significantly influence biomarker levels. The relatively low within-group mean squares (0.170 for PGC1 and 0.207 for SIRT1) suggest acceptable internal consistency within groups.

Table (2). One-Way ANOVA for Comparison of PGC1 and SIRT1 Across Groups.

Variable	Source	SS	df	MS	F	p-value
PGC1	**Between Groups**	**11.906**	**2**	**5.953**	**35.03**	**<0.001**
	Within Groups	**14.787**	**87**	**0.170**	**—**	**—**
SIRT1	**Between Groups**	**11.928**	**2**	**5.964**	**28.86**	**<0.001**
	Within Groups	**17.977**	**87**	**0.207**	**—**	**—**

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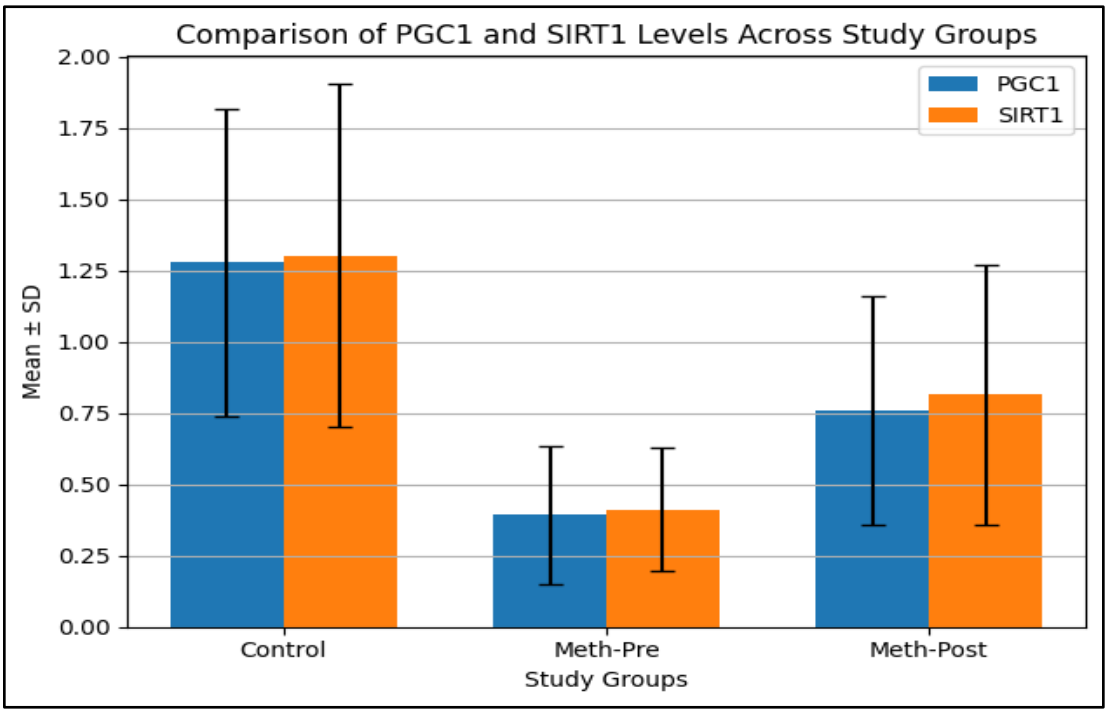

Figure 2: Comparison of PGC1 and SIRT1 Across Groups

DISCUSSION

The significant reduction of Superoxide Dismutase (SOD) in the METH group (2.83 \pm 1.01{ U/mL}) compared to the control (4.76 \pm 0.85{ U/mL}) indicates severe impairment of the first line of enzymatic defense. METH is known to induce superoxide radical production, which overwhelms endogenous SOD. AST treatment showed a partial but significant recovery (3.94 \pm 1.29 { U/mL}).

Interestingly, Catalase levels were significantly elevated in the METH group (56.07 \pm 16.24{ U/mL}), which likely represents a compensatory mechanism to handle the hydrogen peroxide surge. AST treatment partially normalized this (46.00 \pm 13.48{ U/mL}), suggesting a reduction in the overall oxidative load.

These findings align with research showing that AST upregulates antioxidant enzymes via the SIRT1 pathway. SIRT1 deacetylates PGC-1α, which in turn enhances the transcription of SOD and Catalase. Previous studies have demonstrated that AST protects neural cells from oxidative damage by stabilizing this specific signaling pathway (11).

The depletion of GSH in METH-treated patients (3.76 \pm 1.26 \ \mu\text{mol/L}) is a hallmark of non-enzymatic antioxidant exhaustion. Astaxanthin administration resulted in a near-complete restoration of GSH levels (6.27 \pm 1.55 \mu {mol/L}), reaching values statistically comparable to the control group.

AST's ability to restore GSH is well-documented due to its unique chemical structure, which allows it to span the cell membrane and neutralize free radicals more effectively than other carotenoids. Studies on neurotoxicity have shown that AST increases the expression of \gamma-glutamylcysteine synthetase, the rate-limiting enzyme in GSH synthesis (12).

a key marker of lipid peroxidation, was markedly elevated in the METH group (5.97 \pm 1.98 \ { nmol/mL}), confirming extensive damage to neuronal membranes. AST treatment significantly attenuated this damage (4.38 \pm 1.28 { nmol/mL}), although it did not return to baseline.

The reduction in MDA levels supports the hypothesis that AST protects the lipid bilayer from METH-induced ROS. Since PGC-1α also regulates mitochondrial biogenesis, the reduction in MDA may be a result of improved mitochondrial efficiency and reduced "leakage" of reactive species (13).

The data shows a drastic reduction in SIRT1 levels from 1.30 \pm 0.60 in the control group to 0.41 \pm 0.22 in the METH-Pre group. Similarly, PGC-1α levels dropped from 1.28 \pm 0.54 to 0.39 \pm 0.24.

METH is known to cause mitochondrial dysfunction and severe oxidative stress. This downregulation suggests that METH inhibits the SIRT1 deacetylase activity, which is crucial for activating PGC-1α. Without active PGC-1α, the cell loses its ability to regulate mitochondrial biogenesis and the transcription of key antioxidant enzymes (like SOD and Catalase), leading to the oxidative damage observed in your previous results (14) Astaxanthin-Mediated Recovery (The SIRT1/PGC-1α Activation) Following AST treatment (METH-Post group), there was a significant elevation in both markers: SIRT1 rose to 0.81 \pm 0.46 and PGC-1α to 0.76 \pm 0.40 ($p < 0.001$).

This recovery suggests that Astaxanthin acts as a SIRT1 activator. By restoring SIRT1 levels, AST facilitates the deacetylation and subsequent activation of PGC-1α. This molecular "switch" is likely responsible for the improved antioxidant profile (increased SOD/GSH and decreased MDA) seen in your other results. AST doesn't just scavenge radicals; it reprograms the cell's internal defense mechanism via this axis (12).

CONCLUSION

Our study provides compelling evidence that Astaxanthin (AST) acts as a potent neuroprotective agent in the context of methamphetamine (METH) dependence by modulating the SIRT1/PGC-1α signaling pathway. The findings demonstrate that METH exposure significantly suppresses the expression of SIRT1 and PGC-1α, leading to a breakdown in mitochondrial homeostatic control and a subsequent surge in oxidative damage, as evidenced by depleted glutathione levels and elevated lipid peroxidation.

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