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AMELIORATIVE EFFECTS OF VITAMIN E ON SODIUM ARSENITE-INDUCED HEMATOLOGICAL ALTERATIONS AND INFLAMMATION IN WISTAR RATS

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Abstract
Chronic exposure to sodium arsenite (SA), a common environmental pollutant, induces systemic toxicity characterized by hematological dysregulation and organ-specific inflammation, primarily through oxidative stress pathways. Vitamin E (α-tocopherol) is a potent lipid-soluble antioxidant with potential protective effects against such toxicity. This study investigated the ameliorative impact of Vitamin E on SA-induced hematological alterations and inflammatory indices in Wistar rats. Thirty-five male Wistar rats (150-180g) were randomly divided into five groups (n=7). Group A (Control) received corn oil (2ml/kg), Group B received Vitamin E (50 mg/kg), Group C received SA (10 mg/kg), Group D received SA (10 mg/kg) + Vitamin E (25 mg/kg), and Group E received SA (10 mg/kg) + Vitamin E (50 mg/kg). All treatments were administered orally for 14 days. Animals were sacrificed, and blood and organs (heart, kidney) were collected for analysis of hematological indices, nitrite levels, myeloperoxidase (MPO) activity, and reactive oxygen and nitrogen species (RONS). SA exposure caused significant ($p<0.05$) hematotoxicity (anemia, leukocytosis, neutrophilia, lymphopenia) and elevated inflammatory markers (nitrite, MPO, RONS) in the heart and kidney. Co-administration of Vitamin E, particularly at 50 mg/kg, dose-dependently and significantly ($p<0.05$) reversed these SA-induced alterations, restoring hematological parameters and attenuating inflammatory and oxidative stress markers. The findings demonstrate that Vitamin E exerts a potent protective effect against sodium arsenite-induced toxicity by ameliorating hematological abnormalities and mitigating inflammation and oxidative stress.

Keywords: *Sodium arsenite, Vitamin E, Hematology, Inflammation, Oxidative stress, Wistar rats*

Introduction

Arsenic, a pervasive environmental toxicant, represents a significant global health concern due to its presence in contaminated groundwater and industrial effluents (World Health Organization, 2021). Chronic exposure to inorganic arsenic, primarily in the form of sodium arsenite, is linked to a wide spectrum of deleterious health effects, including carcinogenesis, multi-organ damage, and systemic toxicity (Hughes *et al*., 2011). The pathophysiological mechanisms underlying arsenic toxicity are

multifaceted, but a primary driver is the induction of severe oxidative stress and inflammatory cascades (Jomova *et al*., 2011). Sodium arsenite disrupts cellular redox homeostasis by generating reactive oxygen and nitrogen species (RONS), leading to lipid peroxidation, protein denaturation, and DNA damage (Flora, 2011). This oxidative assault subsequently triggers a pronounced inflammatory response, characterized by the activation of immune cells and the release of pro-inflammatory mediators, which perpetuates tissue injury (Dangleben *et al*., 2013).

The deleterious impact of sodium arsenite extends to the hematopoietic system, where it can induce significant hematological dysregulation (Mazumder, 2005). Concurrently, sodium arsenite exposure provokes a robust inflammatory response in vital organs such as the heart and kidney, marked by increased neutrophil infiltration, elevated nitrosative stress, and heightened RONS production (Manna *et al*., 2008). These parallel pathologies in the blood and solid organs underscore the systemic nature of arsenic toxicity.

In light of this pathophysiology, therapeutic strategies aimed at mitigating arsenic-induced toxicity have focused on agents with potent antioxidant and anti-inflammatory properties (Flora, 2011). Vitamin E (α-tocopherol), a lipid-soluble chain-breaking antioxidant, is a prime candidate (Brigelius-Flohé and Traber, 1999). Its primary mode of action involves scavenging peroxyl radicals, terminating lipid peroxidation chain reactions, and modulating signal transduction pathways related to inflammation and cell proliferation (Pekmezci, 2011). By stabilizing cellular membranes and inhibiting the activation of key transcription factors like NF-κB, Vitamin E has the potential to counteract both the oxidative insult and the subsequent inflammatory sequelae initiated by sodium arsenite (Singh *et al*., 2005).

Therefore, this study sought to investigate the ameliorative effects of Vitamin E on sodium arsenite-induced hematological alterations and inflammation in Wistar rats.

Materials and Methods

Chemicals and Reagents

Sodium arsenite ($NaAsO_2$) and Vitamin E (α-Tocopherol) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Commercial assay kits for the determination of nitrite, myeloperoxidase (MPO) activity, and protein concentration were sourced from reputable suppliers. All other chemicals and solvents used were of analytical grade. Corn oil was obtained locally and used as the vehicle.

Animals and Ethical Approval

Healthy adult male Wistar rats (n=35) weighing 150-180 g were procured from the Anatomy Animal House, College of Medicine, University of Benin, Nigeria. The animals were acclimatized for one week under standard laboratory conditions: temperature of 25 ± 2°C, relative humidity of 55 ± 5%, and a 12-hour light/dark cycle. They were housed in polypropylene cages with sterile paddy husk bedding and provided with a standard rodent pellet diet and water ad libitum. All experimental procedures were conducted following the regulations governing the care and use of experimental animals (NIH, 1985). The Faculty of Life Sciences' Ethics Committee approved the animal research with approval number LS21046.

Experimental Design

After acclimatization, the rats were weighed and randomly assigned into five groups (n=7 per group). The treatment regimen, administered orally via gavage for a period of 14 consecutive days, was as follows:

Group A (Control): Received 2 ml/kg body weight of corn oil (vehicle).

Group B (Vitamin E Control): Received Vitamin E (50 mg/kg body weight) dissolved in corn oil.

Group C (Sodium Arsenite - SA): Received Sodium Arsenite (10 mg/kg body weight) dissolved in distilled water.

Group D (SA + Vit E 25): Received co-administration of Sodium Arsenite (10 mg/kg) and Vitamin E (25 mg/kg).

Group E (SA + Vit E 50): Received co-administration of Sodium Arsenite (10 mg/kg) and Vitamin E (50 mg/kg).

The doses and duration were selected based on preliminary studies and relevant literature. All solutions were prepared fresh daily.

Sample Collection and Preparation

Twenty-four hours after the last administration, animals were fasted overnight and humanely sacrificed by cervical dislocation under mild anesthesia. Blood was collected directly from the heart into non-heparinized tubes, allowed to clot, and centrifuged at 4000 × g for 10 min at 4°C to obtain clear serum, which was stored at -20°C for subsequent hematogical analysis.

The heart and kidney were rapidly excised, washed in ice-cold 1.15% potassium chloride (KCl) solution, blotted dry, and weighed. Portions of each organ were either:

1. Fixed in 10% neutral buffered formalin for histopathological processing.
2. Homogenized in appropriate cold phosphate buffer (pH 7.4) using a Teflon homogenizer.

The homogenates were centrifuged at 12,000 × g for 15 minutes at 4°C, and the resultant post-mitochondrial supernatant (PMS) was aliquoted and stored at -80°C for the analysis of various parameters.

Analytical Procedures

Hematological Analysis: A complete blood count (CBC) was performed on whole blood using an automated hematology analyzer. Parameters assessed included Red Blood Cell count (RBC), Hemoglobin concentration (Hb), White Blood Cell count (WBC), and Differential Leukocyte Count (Neutrophils, Lymphocytes, Monocytes).

Assessment of Inflammatory and Oxidative Stress Markers

Tissue nitrite concentration was estimated in the heart and kidney PMS using the Griess reaction method (Green *et al*., 1982) and expressed as units per milligram of protein. Myeloperoxidase (MPO) activity was assayed in the heart and kidney PMS according to the method of Bradley *et al*. (1982) and expressed as units per milligram of protein.

Reactive Oxygen and Nitrogen Species (RONS) generation was measured in the heart and kidney PMS using the 2',7'-dichlorofluorescein diacetate (DCFH-DA) assay. Fluorescence intensity was expressed as a percentage of the control value.

Data Analysis

All data are presented as Mean ± Standard Deviation (SD) for seven animals per group (n=7). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test for multiple comparisons. The statistical significance level was set at $p < 0.05$. Analyses were

conducted using GraphPad Prism software (Version 8.0, GraphPad Software Inc., USA).

Results

Ameliorative Effect of Vitamin E on Hematological Indices

The effects are summarized in Table 1. Administration of sodium arsenite alone (Group C) induced severe hematological toxicity, characterized by a significant (*p < 0.05*) decrease in RBC count and Hb (anemia), and a significant leukocytosis with neutrophilia and lymphopenia. The neutrophil-to-lymphocyte ratio (NLR) was markedly elevated. Co-administration of Vitamin E significantly and dose-dependently reversed these abnormalities, with Group E (50 mg/kg Vit E) showing the most potent effect.

Table 1: Effect of Vitamin E on Sodium Arsenite-induced Alterations in Hematological Indices

Parameters	Grp A	Grp B	Grp C	Grp D	Grp E
RBC (10^6/µl)	12.20 ± 2.2	12.15 ± 2.1	8.06 ± 2.4*	9.78 ± 1.2[a]	10.72 ± 2.1[b]
Hb (g/dl)	29.48 ± 2.3	29.90± 2.5	13.82 ± 2.2*	20.09 ± 1.6[a]	22.80 ± 2.8[b]
WBC (10^3/µl)	6.25 ± 1.1	7.04 ± 1.2	18.35 ± 2.2*	12.10 ± 1.3[a]	10.36 ± 1.1[b]
Neutrophil (%)	12.30 ± 1.2	13.05 ± 2.1	42.04 ± 1.1*	34.56 ± 2.2[a]	21.29 ± 1.3[b]
Lymphocytes (%)	20.82 ± 2.3	20.01 ± 1.9	9.81 ± 1.0*	13.12 ± 1.3[a]	17.13 ± 1.0[b]
Neutrophil/Lymphocytes Ratio	1.90 ± 0.6	1.84 ± 0.2	15.28 ± 1.2*	10.36 ± 0.2[a]	6.66 ± 0.5[b]
Monocytes (%)	2.6 ± 0.1	2.7 ± 0.1	0.5 ± 0.1*	1.5 ± 0.1[a]	2.0 ± 0.2[b]

Grp A=Control, Grp B=Vitamin E, Grp C=Sodium Arsenite, Grp D=Sodium Arsenite+Vit E (25mg/kg), Grp E=Sodium Arsenite+Vit E (50mg/kg). Values are expressed as mean ± standard deviation; n = 7 *Significant as compared with control; $p < 0.05$; [a,b] Significant as compared with Sodium Arsenite; $p < 0.05$.

Ameliorative Effect of Vitamin E on Inflammatory Indices

Sodium arsenite exposure provoked a significant inflammatory response in cardiac and renal tissues (Tables 2, 3, 4). A significant (*p < 0.05*) increase in tissue nitrite, MPO activity, and RONS generation was observed in Group C compared to controls. Co-treatment with Vitamin E significantly (^a,b *p < 0.05*) and dose-dependently reduced these elevations.

Table 2: Effect on Tissue Nitrite Level (units/mg protein)

Nitrite level(units/mg protein)	Grp A	Grp B	Grp C	Grp D	Grp E
Heart	16.15 ± 1.23	15.25 ± 1.03	39.34 ± 2.47*	30.00 ± 1.33[a]	22.25 ± 2.03[b]
Kidney	10.20 ± 1.15	10.22 ± 1.80	20.54 ± 2.41*	17.12 ± 2.11[a]	14.11 ± 1.20[b]

Grp A=Control, Grp B=Vit E, Grp C=Sodium Arsenite, Grp D=Sodium Arsenite+Vit E (25mg/kg), Grp E=Sodium Arsenite+Vit E (50mg/kg). Values are expressed as mean ± standard deviation; n = 7 *Significant as compared with control; $p < 0.05$; [a,b] Significant as compared with Sodium Arsenite; $p < 0.05$.

Table 3: Effect on Tissue Myeloperoxidase Activity (units/mg protein)

Myeloperoxidase (units/mg protein)	**Grp A**	**Grp B**	**Grp C**	**Grp D**	**Grp E**
Heart	11.22 ± 1.03	11.05 ± 1.13	20.91 ± 1.16*	16.17 ± 1.23[a]	13.07 ± 1.08[b]
Kidney	6.01 ± 1.12	5.52 ± 0.19	25.00 ± 2.26*	16.83 ± 1.30[a]	10.12 ± 2.03[b]

Grp A=Control, Grp B=Vit E, Grp C=Sodium Arsenite, Grp D=Sodium Arsenite+Vit E (25mg/kg), Grp E=Sodium Arsenite+Vit E (50mg/kg). Values are expressed as mean ± standard deviation; n = 7 *Significant as compared with control; $p < 0.05$; [a,b] Significant as compared with Sodium Arsenite; $p < 0.05$.

Table 4: Effect on Tissue RONS Generation (% of control)

RONS (DCF fluorescence % of control)	**Grp A**	**Grp B**	**Grp C**	**Grp D**	**Grp E**
Heart	7.71 ± 2.21	6.99 ± 1.21	28.09 ± 2.30*	20.45 ± 1.41[a]	14.29± 2.21[b]
Kidney	1.20 ± 0.10	1.24 ± 0.20	20.09 ± 1.29*	13.09 ± 1.21[a]	9.50 ± 0.41[b]

Grp A=Control, Grp B=Vit E, Grp C=Sodium Arsenite, Grp D=Sodium Arsenite+Vit E (25mg/kg), Grp E=Sodium Arsenite+Vit E (50mg/kg). Values are expressed as mean ± standard deviation; n = 7 *Significant as compared with control; $p < 0.05$; [a,b] Significant as compared with Sodium Arsenite; $p < 0.05$.

Discussion

The present study demonstrates that sodium arsenite (SA) exposure induces profound hematological dysregulation and systemic inflammation, and co-administration of Vitamin E provides significant, dose-dependent amelioration. The induction of anemia aligns with the documented hematopoietic toxicity of arsenic (Mazumder, 2005), likely due to oxidative hemolysis and bone marrow suppression (Jomova *et al*., 2011). Vitamin E's efficacy in restoring these parameters can be attributed to its membrane-stabilizing and radical-scavenging role (Brigelius-Flohé and Traber, 1999).

Concurrently, the observed leukocytosis with neutrophilia and lymphopenia indicates a severe systemic inflammatory state. The dramatic increase in the neutrophil-to-lymphocyte ratio (NLR) serves as a key inflammatory index (Zahorec, 2021). Vitamin E's ability to normalize the WBC differential and lower the NLR highlights its immunomodulatory properties, potentially via suppression of pro-inflammatory pathways like NF-κB (Singh *et al*., 2005; Pekmezci, 2011).

The systemic inflammation was corroborated by organ-specific biochemical markers. The significant elevations in cardiac and renal nitrite levels, MPO activity, and RONS generation in the SA group link oxidative stress to tissue injury. Increased nitrite and RONS can lead to cytotoxic peroxynitrite formation (Flora, 2011), while elevated MPO activity indicates neutrophil infiltration (Bradley *et al*., 1982). Vitamin E's co-administration effectively reversed these indices, suggesting a quenching of reactive species and a downregulation of inflammatory cell recruitment, consistent with its established antioxidant and anti-inflammatory actions (Singh *et al*., 2005). The superior efficacy of the 50 mg/kg dose underscores the dose-responsive nature of its protective effect.

Conclusion

In conclusion, Vitamin E significantly attenuates sodium arsenite-induced hematotoxicity and inflammation. It restores normal hematological profiles and dampens inflammatory and oxidative stress responses in the heart and kidney. These findings position Vitamin E as a promising therapeutic adjunct for mitigating the toxicological consequences of arsenic exposure.

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