PROTECTIVE EFFECTS OF *VITAMIN E* ON SODIUM ARSENITE-INDUCED ALTERATIONS IN HAEMATOLOGICAL PARAMETERS IN WISTAR RATS

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BENIN CITY

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A PROJECT SUBMITTED TO THE DEPARTMENT OF MEDICAL BIOCHEMISTRY, SCHOOL OF BASIC MEDICAL SCIENCES, IN PARTIAL FUFILMENT OF THE REQUIREMENT FOR THE

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CERTIFICATION.

This is to certify that this research work was carried out by **OGHENETEGA PHILADELPHIA AKPESIRI,** with Matriculation Number: **(BMS2101433),** a student of the Department of Medical Biochemistry, School of Basic Medical Sciences, University of Benin, Benin City under the supervision of **DR. (MRS). O. IKPONMWOSA-EWEKA.**

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EXTERNAL SUPERVISOR **DATE**

DEDICATION

This project is dedicated to Almighty God**,** the source of my wisdom, strength, and perseverance throughout this research work. Without His guidance and grace, this achievement would not have been possible.

I also dedicate this work to my beloved parents, for their endless love, prayers, and sacrifices, which have been my greatest motivation. To my family and friends, thank you for your support, encouragement.

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ABSTRACT

Arsenic exposure remains a major global health challenge, and sodium arsenite is one of the most toxic inorganic arsenic compounds known to cause severe hematological, oxidative, and immunological disturbances. This study examined the protective effects of vitamin E against sodium arsenite–induced changes in hematological parameters in Wistar rats. Thirty-five male rats were randomly divided into five groups of seven: a control group, a vitamin E–only group (50 mg/kg), a sodium arsenite–only group (10 mg/kg), and two co-treatment groups receiving sodium arsenite with either 25 mg/kg or 50 mg/kg of vitamin E. All treatments were given orally for 14 days, after which blood samples were collected for hematological analysis. Results showed that sodium arsenite caused significant hematotoxicity, marked by reductions in red blood cell count (RBC), hemoglobin concentration (Hb), lymphocyte percentage, and monocyte levels, along with increases in white blood cell count (WBC), neutrophil levels, and the neutrophil-to-lymphocyte ratio (NLR). These changes indicate anemia, oxidative stress, inflammation, and immune suppression linked to arsenic toxicity. Co-administration of vitamin E significantly reduced these effects in a dose-dependent manner. The 50 mg/kg dose of vitamin E showed the greatest improvement across all hematological parameters, demonstrating its superior protective effects. The findings suggest that vitamin E effectively reduces sodium arsenite–induced hematological damage through its strong antioxidant, anti-inflammatory, and membrane-stabilizing properties. This study highlights the potential of vitamin E as a natural antioxidant therapy to manage hematotoxicity caused by environmental arsenic exposure.

CHAPTER ONE

INTRODUCTION

1.1 Background of the Study

Arsenic is a naturally occurring metalloid that poses a major global health hazard due to its widespread presence in the environment and its potential to cause severe toxicological effects in humans and animals. Chronic or acute exposure to inorganic arsenic compounds such as sodium arsenite has been associated with multiple organ toxicities, including hematological, hepatic, renal, and cardiovascular dysfunctions (Ola-Davies and Akinrinde, 2016). Among these, hematological disturbances are particularly significant, as the blood serves as a primary medium for the distribution of arsenic and a critical target of its toxic effects.

The hematotoxic effects of sodium arsenite are mediated primarily through oxidative stress, which involves the excessive generation of reactive oxygen species (ROS) leading to lipid peroxidation, protein oxidation, and DNA damage. These oxidative insults disrupt normal hematopoiesis, reduce red blood cell count, and impair the oxygen-carrying capacity of the blood, resulting in anemia and related hematological disorders (Mondal *et al.,* 2016). In addition, arsenic exposure has been reported to alter liver function, further aggravating hematological abnormalities due to impaired synthesis of blood proteins and detoxification processes.

Several studies have examined the use of antioxidants as protective agents against arsenic-induced toxicity. Antioxidants like vitamins C and E have been shown to play a crucial role in neutralizing free radicals and restoring cellular redox balance. Vitamin E (α-tocopherol), a lipid-soluble antioxidant, is especially effective in protecting biological membranes from

oxidative damage by scavenging lipid peroxyl radicals (Mondal *et al.,* 2016). Its protective potential has been demonstrated in various models of arsenic-induced toxicity, where it reduces oxidative stress, prevents apoptosis, and improves hematological and biochemical markers (Oyagbemi *et al.,* 2018). Previous experimental results have shown that co-administering vitamin E can lessen arsenic-induced blood and liver problems, boost antioxidant defenses, and decrease cell damage (Oyagbemi *et al.,* 2018; Ola-Davies and Akinrinde, 2016). These protective effects mainly result from vitamin E's ability to scavenge free radicals and stabilize cell membranes, helping to maintain cellular integrity and function under toxic stress.

Given the growing concern over arsenic contamination and its health effects, using natural or dietary antioxidants offers a promising strategy to lessen its harmful impacts. Therefore, this study aims to evaluate the protective effects of vitamin E on sodium arsenite-induced changes in hematological parameters in Wistar rats, with the goal of gaining deeper insights into its potential therapeutic benefits and mechanisms of action.

1.2 Statement of the Problem

Arsenic contamination remains a significant public health and environmental concern worldwide, particularly in developing regions where exposure through contaminated water, food, and soil is prevalent. Sodium arsenite, a highly toxic inorganic form of arsenic, has been shown to induce multiple systemic toxicities, including hematological and biochemical disturbances, oxidative stress, and tissue damage (Oyibo *et al.,* 2021). The hematological system is especially vulnerable to arsenic toxicity because of the metal’s ability to generate reactive oxygen species (ROS), disrupt antioxidant defense mechanisms, and alter normal blood cell physiology (Basher *et al.,* 2024). These alterations can lead to anemia, leukopenia, and other blood-related disorders

that compromise overall health and homeostasis. Despite extensive research on the toxic effects of arsenic, effective and affordable protective strategies remain limited. Conventional chelation therapies, though useful in certain cases, are often associated with adverse effects and limited accessibility. As a result, attention has shifted towards natural and nutritional antioxidants as safer alternatives for mitigating arsenic-induced toxicity. Several studies have reported that bioactive compounds and antioxidants such as vitamin E, selenium, and plant extracts possess potent protective effects against arsenic-induced oxidative and hematological damage (Oyibo, 2021; Basher *et al.*, 2024).

Vitamin E (α-tocopherol), a lipid-soluble antioxidant, plays a vital role in protecting cellular membranes and biomolecules from oxidative damage by scavenging free radicals and preventing lipid peroxidation. However, despite its known antioxidant properties, there is still limited experimental evidence explaining the specific protective effects of vitamin E against sodium arsenite-induced changes in hematological parameters, especially in Wistar rats, which are commonly used as a standard model in toxicological studies.

1.3 Aim of Study

This study aims to assess the protective effects of vitamin E against sodium arsenite-induced changes in hematological parameters in Wistar rats. It also examines whether vitamin E supplementation can mitigate the toxic effects of sodium arsenite on blood components and restore normal hematological functions, providing insights into its potential as a therapeutic agent against arsenic-induced hematotoxicity.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Overview of Arsenic and Sodium Arsenite

Arsenic is a naturally occurring metalloid that is widely spread across the earth's crust and is recognized as one of the most important global environmental toxicants affecting human, animal, and ecological health. According to (Genchi *et al.,* 2022), arsenic remains a "major worldwide health issue" because of its ubiquity, persistence, and high mobility in the environment, especially in groundwater systems used for drinking and agriculture. Arsenic exists in multiple oxidation states (−3, 0, +3, and +5), but the inorganic forms—arsenite (As^{3+}) and arsenate (As^{5+})—are the most toxic and biologically active species (Biswas *et al.,* 2021). Among these, trivalent arsenite, especially in the form of sodium arsenite ($NaAsO_2$), shows the highest level of toxicity because of its strong attraction to sulfhydryl-containing biomolecules, its ability to easily cross cell membranes, and its capacity to cause severe oxidative and metabolic disturbances (Ganie *et al.,* 2024). Sodium arsenite is a soluble inorganic arsenic compound often used as a reference toxicant because of its quick absorption, strong reactivity, and well-known toxicological profile (Zargari, 2021). Its widespread presence in contaminated water, soil, and agricultural environments makes it a significant contributor to chronic arsenic exposure in many parts of the world (Genchi *et al.,* 2022; Biswas *et al.,* 2021).

FIGURE 2.1: PURE FORM OF SODIUM ARSENITE (Biswas *et al.,* 2021)

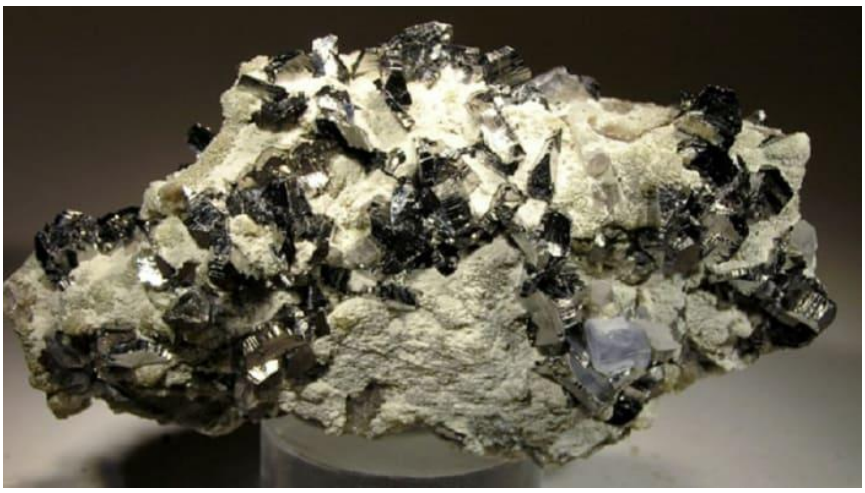

FIGURE 2.2: Oxidative State of Sodium Arsenite (Genchi *et al.,* 2022)

2.1.1 Natural and Human Sources of Arsenic

Arsenic enters the environment through both natural geological processes and human industrial activities. Naturally, it exists in rocks, sulfide ores, volcanic emissions, geothermal waters, and sediments. Ganie *et al.,* (2024) identify weathering, erosion, the dissolution of arsenic-bearing minerals, and geothermal processes as key natural mechanisms that release

arsenic into groundwater aquifers. This natural contamination explains why arsenic levels in well water can be extremely high even in rural areas with no industrial activity. Human activities significantly increase environmental arsenic contamination. Mining and smelting operations release large amounts of arsenic into nearby soils and water sources (Biswas *et al.,* 2021). Burning fossil fuels, especially coal, also contributes to atmospheric deposition of arsenic particles. Historically, arsenic-based pesticides, herbicides, rodenticides, and wood preservatives such as chromated copper arsenate (CCA) have been major contributors in agriculture (Zargari, 2021).

Industrial activities such as glass manufacturing, semiconductor production, metal alloy fabrication, and pharmaceutical formulations further introduce arsenic into the environment (Genchi *et al.,* 2022). Because arsenic is highly mobile, it infiltrates groundwater and moves through soil layers, eventually entering the food chain. (Genchi *et al.,* 2022) emphasize that crops, especially rice, have a significant tendency to absorb arsenic from contaminated irrigated water, posing a substantial dietary exposure risk.

Therefore, the combined effect of natural and human-made sources leads to ongoing arsenic exposure in many nations across Asia, Africa, and Latin America, resulting in a continuous global health issue (Zargari, 2021).

2.1.2 Chemical Nature and Behavior of Arsenic

Arsenic has unique physicochemical properties that affect its environmental behavior, reactivity, toxicity, and bioavailability. As a metalloid, it shows both metallic and non-metallic traits, making it highly versatile in forming various chemical species (Genchi *et al.,* 2022). The form in

which arsenic exists mostly depends on environmental factors like pH, temperature, redox potential, and microbial activity (Zargari, 2021). Under reducing (anaerobic) conditions, arsenite (As^{3+}) is predominant. This form is very toxic because it mainly exists as arsenious acid (H_3AsO_3), a neutral molecule that can easily diffuse across biological membranes (Ganie *et al.,* 2024). Under oxidizing (aerobic) conditions, arsenate (As^{5+}) becomes the dominant form and behaves similarly to phosphate, often disrupting phosphate-dependent metabolic pathways. The high mobility of arsenite is a key reason why sodium arsenite contamination spreads quickly in soils and aquatic systems. Additionally, the trivalent state of arsenic forms stable complexes with thiol groups in proteins and enzymes, making arsenite much more reactive and toxic than arsenate (Biswas *et al.,* 2021).

2.1.3 Biotransformation and Metabolism of Arsenic

Once absorbed, arsenic undergoes extensive biotransformation, mainly through oxidation-reduction reactions and methylation processes that occur primarily in the liver. The classical metabolic pathway converts inorganic arsenite (As^{3+}) and arsenate (As^{5+}) into monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) using the enzyme arsenic (+3 oxidation state) methyltransferase (AS3MT) (Genchi *et al.,* 2022). While methylation was historically regarded as a detoxification process, newer evidence indicates that several intermediate metabolites—especially MMA(III) and DMA(III)—are more reactive and toxic than the original compounds (Ganie *et al.,* 2024). These intermediates generate reactive oxygen species (ROS), cause mitochondrial dysfunction, promote lipid peroxidation, and directly damage DNA and proteins (Zargari, 2021).

Arsenic's high affinity for sulfhydryl groups further increases its toxicity. (Biswas *et al.,* 2021) report that arsenite binds strongly to –SH groups in vital metabolic enzymes, causing enzyme inactivation, blocking oxidative phosphorylation, depleting intracellular glutathione (GSH), and disrupting ATP production. This biochemical interference affects multiple metabolic pathways, including glycolysis, the TCA cycle, and cellular antioxidant defenses. Arsenic metabolites are eventually excreted in urine; however, chronic exposure leads to tissue buildup, especially in the liver, kidneys, skin, hair, and nails (Genchi *et al.,* 2022).

2.1.4 Sodium Arsenite: Structure, Properties, and Toxicological Significance

Sodium arsenite ($NaAsO_2$) is one of the most toxic and heavily studied inorganic arsenic compounds. Its high water solubility, quick dissociation into trivalent arsenite ions, and strong reactivity with biological molecules make it a highly systemic toxicant (Zargari, 2021).

Key characteristics include:

- It exists predominantly in the highly toxic trivalent form (As^{3+}).
- It is rapidly absorbed through the gastrointestinal tract and respiratory system.
- It crosses cell membranes easily due to the uncharged nature of arsenious acid.
- It disrupts cellular redox balance, energy metabolism, and antioxidant systems (Genchi *et al.,* 2022).
- It induces significant oxidative stress, inflammation, genotoxicity, and metabolic disturbances (Ganie *et al.,* 2024).

Because sodium arsenite mimics naturally occurring geogenic arsenite species, it is commonly used in experimental toxicology to model arsenic-induced oxidative stress, hepatotoxicity,

nephrotoxicity, cardiovascular dysfunction, endocrine disruption, and carcinogenesis (Biswas *et al.,* 2021; Ganie *et al.,* 2024).

2.1.5 Health Effects of Long-Term Exposure to Sodium Arsenite

2.1.5.1 Oxidative Stress and Antioxidant Depletion

Sodium arsenite causes a significant rise in ROS production, leading to lipid peroxidation, DNA fragmentation, protein oxidation, and mitochondrial dysfunction (Zargari, 2021).

2.1.5.2 Inflammation and Immune Dysregulation

It activates NF-κB and MAPK pathways, causing chronic inflammation and cytokine release (Biswas *et al.,* 2021).

2.1.5.3 Cardiovascular Toxicity

Recent evidence from Balarastaghi *et al.*, (2023) indicates that sodium arsenite is a major cause of hypertension and atherosclerosis through endothelial dysfunction, nitric oxide depletion, and vascular oxidative injury.

2.1.5.4 Hepatic and Renal Toxicity

The liver and kidneys accumulate arsenic, leading to hepatocellular damage, fibrosis, tubular necrosis, and decreased filtration (Genchi *et al.,* 2022; Ganie *et al.,* 2024).

2.1.5.5 Carcinogenesis

Long-term exposure is associated with cancers of the skin, bladder, liver, and lungs due to genotoxic and epigenetic changes (Genchi *et al.,* 2022).

2.2 Sources of Sodium Arsenite

Sodium arsenite ($NaAsO_2$) is an inorganic arsenic compound known for its environmental persistence and high toxicity. Its presence in the environment results from both natural processes and human activities, which significantly contribute to arsenic contamination of water, soil, and living systems (Patel *et al.,* 2023).

1. Natural Sources

Although less common than human-derived contamination, certain natural processes release inorganic arsenic, including sodium arsenite, into the environment:

- **Geological weathering:** Weathering of arsenic-containing minerals such as arsenopyrite releases arsenite (As^{3+}) into surrounding water bodies. This is a major global source of groundwater contamination (Patel *et al.,* 2023).
- **Volcanic activity:** Volcanic eruptions emit arsenic gases and particulates that settle into soils and water.
- **Biogeochemical cycling:** Microbial reduction of arsenic compounds in sediments can convert arsenate (As^{5+}) to the more toxic arsenite (As^{3+}), including sodium arsenite.

2. Anthropogenic (Human-Related) Sources

Human activities are the main and most important sources of sodium arsenite in ecosystems. These include:

Industrial Processes

- **Mining and smelting:** Extraction and refining of metals like gold, copper, and lead release high levels of inorganic arsenic that can convert into sodium arsenite in water environments (Ganie *et al.,* 2024).
- **Coal combustion:** Burning fossil fuels releases arsenic-rich fly ash that pollutes the air, water, and soil..
- **Glass and semiconductor industries:** Sodium arsenite can be used or produced in the manufacturing of industrial chemicals and electronic parts.

Agricultural Uses

Historically, sodium arsenite was widely used as:

- **Pesticide/herbicide**, especially in cotton farming and orchard cultivation.
- **Wood preservative**, preventing fungal decay. Though largely restricted today, residues persist in soils and groundwater for decades (Patel *et al.,* 2023).

Pharmaceutical and Veterinary Applications

In the past, arsenite-based compounds were used in:

- Animal feed additives
- Anti-parasitic drugs

These uses have declined, but contamination remains in old agricultural lands.

Waste Disposal and LeachingG

- Improper disposal of arsenic-containing industrial waste, batteries, and chemical residues leads to leaching of sodium arsenite into soil and water.
- Landfills and poorly managed dumpsites serve as long-term contamination points.

2.3 Exposure Routes of Sodium Arsenite

Exposure to sodium arsenite happens mainly through ingestion, inhalation, and skin contact. Because sodium arsenite is highly soluble in water, exposure is common in contaminated areas.

2.3.1 Ingestion (Oral Route)

The primary and most dangerous exposure route is ingestion of contaminated food and water.

- **Drinking contaminated groundwater:** Many regions rely on arsenic-contaminated boreholes and wells.
- **Food chain bioaccumulation:** Plants irrigated with contaminated water (e.g., rice, vegetables) accumulate arsenite, making dietary intake a common exposure pathway (Patel *et al.,* 2023).
- **Livestock products:** Animals drinking arsenic-containing water accumulate it in milk, meat, and organs.

This route is linked to systemic toxicity that affects the liver, kidney, brain, reproductive organs, and hematological system (Akbari *et al.,* 2022; Nikravesh *et al.,* 2023).

2.4 Toxicokinetics of Sodium Arsenite

Toxicokinetics describes how toxins interact with the body from the point of exposure to their internal movement and final disposition (Bibi *et al*.). Sodium arsenite follows toxicokinetic patterns similar to other metals and arsenic compounds that have been studied under controlled laboratory conditions. These patterns include relative bioavailability, dynamic changes, biotransformation, and bioaccumulation within biological systems.

Studies on arsenic compounds show that, after entering an organism, they undergo toxicokinetic processes validated through intra- and inter-laboratory studies, especially concerning soil arsenic relative bioavailability in mice (Bradham *et al.,* 2020). Similarly, sodium arsenite becomes available within tissues following exposure, and its internal concentration depends on the form of arsenic, its potency, and interactions with biological systems. Toxicokinetic sensitivity to metals—including arsenic—is often influenced by toxicokinetic and toxicodynamic parameters, which explain variations in biological response across species (Yang *et al.,* 2021). For example, zebrafish larvae exposed to metals show differences in internal concentrations due to variations in uptake and internal distribution. Sodium arsenite behaves similarly, exhibiting a movement pattern that determines how quickly it enters tissues and how long it stays active.

A major toxicokinetic feature of sodium arsenite is its dynamic changes of arsenic biotransformation, as observed in freshwater fish such as crucian carp under chronic dietborne exposure (Cui *et al.,* 2021). These dynamic changes include time-dependent alterations in the internal chemical form of arsenic and a progressive bioaccumulation in muscle, reflecting long-

term storage and persistence in biological tissues. Toxicokinetics of trivalent metals often involve unique properties of potency and interactions, such as those reported in metal mixtures in Drosophila (Beamish *et al.,* 2021). Sodium arsenite expresses similar toxicokinetic behavior, as its interactions at the molecular level influence how it moves within tissues, how much accumulates, and how strongly it binds to internal targets. These toxicokinetic interactions ultimately contribute to its overall toxicity.

2.5 TOXICODYNAMICS OF SODIUM ARSENITE

Toxicodynamics explains how toxins interact with the body to cause harmful biological effects (Bibi *et al*.). The toxicodynamic actions of sodium arsenite are closely linked to its toxicokinetic behavior because the internal concentration, bioaccumulation, and biotransformation determine how it interacts with key biological targets. Sodium arsenite shows toxicodynamic features similar to those seen in studies of developmental toxicology of metal mixtures. In Drosophila, metals display unique potency and interaction properties, which are crucial in shaping their overall biological effects (Beamish *et al.,* 2021). Sodium arsenite exhibits similar toxicodynamic behavior, where its molecular potency and interactions generate harmful downstream effects.

According to (Yang *et al.,* 2021), both toxicokinetic and toxicodynamic parameters work together to determine the sensitivity of organisms, especially in models like zebrafish larvae exposed to metals. These parameters influence how sodium arsenite disrupts internal functions once it reaches its target sites. The toxicodynamic impact of arsenic compounds includes dynamic changes in tissues, reflecting both biotransformation and functional changes (Cui *et al.,* 2021). In the case of sodium arsenite, these effects become more evident under chronic exposure conditions, where arsenic buildup in tissues leads to increased disruption of normal biological

processes. Because sodium arsenite tends to form strong interactions with internal components, its toxicodynamic effects include changes in developmental processes, metabolism, and tissue structure. These outcomes illustrate the interactions described in studies of metal mixture toxicity, where toxicity results from both potency and the combined biochemical interactions of the involved metals.

2.6 HEMATOLOGICAL EFFECTS OF SODIUM ARSENITE

Sodium arsenite is widely recognized as a toxic substance capable of causing significant changes in hematologic parameters, and these effects have been consistently reported across various experimental models. Exposure to sodium arsenite disrupts normal blood functions, leading to measurable changes in hematology indices that indicate systemic toxicity and impaired biological processes. In rats exposed to sodium arsenite, notable hematological effects have been observed, including disruptions in parameters related to immune function and blood cell activity (Ewere *et al.,* 2021). These changes occur because sodium arsenite interferes with blood cell components and impacts the overall hematologic profile, resulting in deviations from normal physiological levels. The hematologic alterations seen in treated rats suggest that sodium arsenite damages blood-forming tissues and modifies circulating blood cells.

Similarly, studies evaluating hematologic parameters in relation to sodium arsenite toxicity in rats have provided clear evidence of adverse effects. (Kaya and Şimşek, 2024) observed that sodium arsenite exposure causes significant changes in hematologic values, indicating that the compound negatively impacts the blood system. The need for protective agents such as royal jelly highlights the extent of hematologic disruption caused by sodium arsenite ingestion. In goats, exposure to sodium arsenite has been shown to affect hematology indices, leading to broad

alterations that reflect compromised blood quality and function (Zubair *et al.,* 2020). These indices serve as biomarkers for toxicity, and the deviations observed in the exposed Teddy goat bucks suggest that sodium arsenite causes systemic hematologic injury. The study also emphasizes that sodium arsenite toxicity extends beyond hematology, impacting reproductive parameters as well; however, the hematologic effects constitute a significant part of the toxicity profile.

Other studies further support the blood disturbances caused by arsenic compounds. Arsenic-induced blood changes have been reported in adult female mice, where exposure led to changes consistent with toxic damage to the blood system (Basher *et al.,* 2024). These blood changes were accompanied by biochemical shifts and organ development abnormalities, indicating that arsenic affects both circulating blood components and internal organs. The study emphasizes that blood parameters are highly sensitive to arsenic toxicity. Although some research focuses on kidney and liver systems, evidence from sodium arsenite exposure shows related changes that can also affect blood components. For instance, sodium arsenite toxicity in rats includes systemic effects seen in multiple organ systems (Gholamine *et al.,* 2021). While kidney and liver toxicity were the main concerns, these systemic toxic effects often occur alongside blood disturbances, further highlighting the broad impact of sodium arsenite.

2.7 OVERVIEW OF VITAMIN E

Vitamin E is a well-known nutrient with a long scientific history and a broad range of biological functions. It has been extensively described as an important compound with diverse roles, and its significance has been recognized over more than a century of research. According to (Khallouki *et al.,* 2020), vitamin E is presented as a vital micronutrient with multiple functional properties,

and a general overview highlights its importance in nutrition and biological systems. Similarly, (Morsy and Alanazi, 2020) provide a brief overview that outlines the key features and main characteristics of this compound. The history and development of vitamin E research span a lengthy period. As noted by (Kowalska, 2024), the vitamin has a clear discovery history, and its scientific understanding has advanced through several stages, including elucidating its mechanism of action, its biological role, and the impacts of deficiency. These elements form crucial parts of the overall review of vitamin E and underscore its significance across various fields of biological and nutritional sciences.

Research on vitamin E has now reached a milestone of over 100 years, reflecting its long-standing significance and the extensive scientific effort to understand its nature (Ralla *et al.,* 2024). This history includes advances in synthesis and formulation, which have improved its availability and use, especially in animal nutrition. The widespread application of vitamin E has made it a key compound in both human and animal health, and its presence in nutritional systems shows its ongoing scientific and practical importance. Recently, the view of vitamin E has broadened. (Ungurianu *et al.,* 2021) note that vitamin E goes beyond its antioxidant label, indicating that it has roles beyond classical antioxidant activity. This wider perspective describes vitamin E as having multiple functions that help with biological regulation and support normal physiological processes. Recognizing that vitamin E has a diverse range of properties has deepened our understanding of its influence within biological systems.

FIGURE 2.3: SOURCES OF VITAMIN E (Ralla *et al.,* 2024)

2.8 Mechanism of Action of Vitamin E In Biological Systems

The mechanism of action of vitamin E in biological systems has been extensively studied, and the literature provides a thorough explanation of how these nutrient functions in various physiological processes. Vitamin E is well known for its roles in antioxidant activity, immune regulation, cardiovascular health, and cellular signaling, all of which underpin its biological significance. A key aspect of vitamin E's mechanism is its long-standing reputation as an antioxidant. According to Blaner *et al.,* (2021), vitamin E has been discussed in the context of determining “the real antioxidant,” highlighting its central role in protecting biological systems from oxidative damage. This antioxidant property has been a fundamental aspect of vitamin E

research and helps maintain cellular stability. However, as noted by (Ungurianu *et al.,* 2021), vitamin E goes beyond its antioxidant label, indicating that its mechanism involves multiple activities that influence biological processes in more complex ways.

In cardiovascular systems, vitamin E acts through mechanisms that influence physiological and biochemical pathways. (Shah *et al.,* 2021) report that vitamin E has various effects on the cardiovascular system, demonstrating that it interacts with cardiovascular tissues in a manner that contributes to functional protection. These effects are linked to its antioxidant activity and to other mechanisms that influence cellular and tissue responses within the cardiovascular environment. Vitamin E also plays an important role in the immune response. According to (Meydani and Blumberg, 2020), vitamin E interacts with immune cells and contributes to the modulation of immune activity. This demonstrates that its mechanism of action is not limited to chemical antioxidant effects but also includes regulation of immune function, an important component of maintaining biological stability under different physiological conditions.

Furthermore, the mechanism of vitamin E involves contributions to anti-inflammatory and antioxidant systems**,** particularly within the context of neurological and psychological function. (Manosso *et al.,* 2022) explain that vitamin E may be relevant in the management of major depressive disorder through these systems, demonstrating its biological actions that influence inflammation and oxidative balance in neural tissues. These observations highlight the broader physiological significance of the mechanisms attributed to vitamin E.

2.9 ANTIOXIDANT PROTECTIVE ROLE OF VITAMIN E

Vitamin E is widely recognized for its essential role as an antioxidant and is consistently described as a key component in protecting biological systems from oxidative damage. (Abdelqader *et al.,* 2023) emphasize that vitamin E plays a vital role in preventing damage caused by free radicals, highlighting its importance in reducing oxidative stress within living organisms. This antioxidant activity enables vitamin E to protect cellular components against the harmful effects of reactive species produced during normal metabolism and under external stress conditions. The antioxidant character of vitamin E has been the subject of extensive discussion in the scientific literature. (Blaner *et al.,* 2021) describe vitamin E in the context of determining "the real antioxidant," highlighting its long-established role as a central component of antioxidant defense systems in biological tissues. This view reinforces the concept that vitamin E has been consistently regarded as a principal antioxidant in nutrition and physiology.

However, the protective role of vitamin E goes beyond traditional antioxidant definitions. (Ungurianu *et al.,* 2021) describe vitamin E beyond its antioxidant label, suggesting that its antioxidant activity is part of a more complex set of biological functions that help maintain cellular stability. This broader view emphasizes the variety of pathways through which vitamin E can act to defend against oxidative disturbances. Vitamin E also serves as an important neuroprotective agent, and this role is primarily linked to its antioxidant properties. (Yap and Lye 2020) offer insight into vitamin E as a neuroprotective compound, demonstrating that its ability to counteract oxidative effects significantly helps protect neural tissues. Through these antioxidant mechanisms, vitamin E helps preserve the integrity of neural cells and supports the stability of nervous system functions.

In aquatic organisms, vitamin E is described as essential for protecting tissues against oxidative damage. (El-Sayed and Izquierdo, 2022) emphasize the importance of vitamin E for farmed fish, showing its antioxidant functions in preventing oxidative harm across different fish species. This role is especially important in environments where oxidative stress is common due to metabolic demands, dietary factors, or environmental conditions.

2.10 INTERACTION BETWEEN SODIUM ARSENITE TOXICITY AND VITAMIN E

The interaction between sodium arsenite toxicity and vitamin E has been extensively studied in various experimental models. The available research consistently shows that vitamin E serves as a significant ameliorating, protective, or mitigating agent against the harmful effects caused by sodium arsenite exposure. Sodium arsenite is known to cause oxidative injury, DNA damage, tissue toxicity, and physiological disruptions, and vitamin E helps counter many of these effects through its biological properties. Mashkoor *et al.,* (2023) demonstrated that arsenic exposure causes oxidative stress and toxicity in broiler chicks, and applying vitamin E significantly reduced these toxic outcomes. Their findings reveal that vitamin E interacts with arsenic-induced oxidative mechanisms and aids in reducing toxicity, emphasizing its protective role during arsenic exposure.

In post-pubertal Wistar rats, (Mondal *et al.,* 2023) reported that vitamin E, when combined with vitamin C, reduces sodium arsenite–induced ovarian DNA damage, follicular atresia, and oxidative injury. This shows a strong interaction between the antioxidant effects of vitamin E and the toxic pathways activated by sodium arsenite. The decrease in DNA damage and oxidative injury suggests that vitamin E blocks sodium arsenite–caused cellular disruption.

Vitamin E has also been linked to protective effects during sodium arsenite–induced gastrointestinal toxicity. (Adebayo-Gege and Olaleye) described that vitamin E helped lessen sodium arsenite toxicity during gastric ulcer healing, supported by molecular docking analyses involving NADPH oxidase. This indicates that vitamin E interacts with molecular pathways affected by sodium arsenite, aiding in reducing toxicity during tissue healing.

In Black Bengal kids, vitamin E has been evaluated in relation to arsenic toxicity. (Satapathy *et al.,* 2021) reported that vitamin E, together with *Saccharomyces cerevisiae* yeast, demonstrated ameliorative efficiency against arsenic toxicity. Their results show that vitamin E interacts with arsenic-associated physiological disturbances, contributing to improved biological responses in treated animals compared to those exposed to arsenic alone. Protective interactions involving vitamin E have also been observed in rodent models exposed to sodium arsenite. (Oyibo *et al.,* 2021), while studying sodium arsenite-induced toxicity in male Wistar rats, described protective outcomes when antioxidant agents were applied. Although their primary focus was the ethanol extract of Vitellaria paradoxa leaves, the study reinforces the idea that antioxidant-based interventions—such as vitamin E—are effective in protecting against sodium arsenite-induced toxicity.

CHAPTER 3

MATERIALS AND METHODS

3.1 Materials

3.2 Chemicals and Reagents

Rutin, Vitamin E, and Sodium arsenite (≥ 96%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other reagents used were of analytical grade and supplied by Sigma-Aldrich (St. Louis, MO, USA) and British Drug Houses (Dorset, Poole, UK).

ANIMAL PROTOCOL

Healthy male Wistar rats weighing 150-180 g were purchased from Central Animal House, Department of Anatomy, University of Benin, Nigeria, for the study. The rats were acclimated for one week after purchase. They were housed in plastic cages in a well-ventilated rat house, provided with rat pellets, and had water ad libitum. They were exposed to a natural photoperiod of 12 hours light and 12 hours dark during the acclimation period and administration of Rutin and Sodium arsenite (SA).

EXPERIMENTAL DESIGN

The animals were randomly divided into five groups of seven animals each and treated as follows:

Group 1: Orally administered corn oil only for 14 days (2 mL/kg body weight)

Group 2: Orally administered 50 mg/kg body weight of Rutin or Vitamin E dissolved in distilled water for 14 days.

Group 3: Orally administered 10 mg/kg body weight of Sodium arsenite (SA) dissolved in distilled water for 14 days.

Group 4: Orally co-administered 25 mg/kg body weight of Rutin or Vitamin E and 10 mg/kg body weight of Sodium arsenite (SA) for 14 days.

Group 5: Orally co-administered 50 mg/kg body weight of Rutin or Vitamin E and 10 mg/kg body weight of Sodium arsenite (SA) for 14 days.

3.3 SACRIFICE OF EXPERIMENTAL ANIMALS

Animals were euthanized by cervical dislocation, and blood was collected into non-heparinized tubes and allowed to clot. The serum was then separated by centrifugation of the clotted blood at 4000 g for 10 minutes using a tabletop centrifuge.

Hematological assay

Packed cell volume (PCV), hemoglobin (Hb), red blood cell (RBC), white blood cell (WBC), platelets, reticulocyte counts and differential white blood cell counts was analyzed using the Beckman Coulter JT series Hematology Analyzer (Jones *et al.,* 1996).

Principle and procedure

The Beckman Coulter method of sizing and counting particles uses measurable changes in electrical resistance produced by nonconductive particles suspended in an electrolyte.

A suspension of blood cells flows through a small orifice while an electric current is applied. A tiny opening (aperture) between electrodes serves as the sensing zone, where suspended particles pass through. In this zone, each particle displaces its volume of electrolyte. Beckman Coulter measures this displaced volume as a voltage pulse, with the pulse height being proportional to the particle's size. The amount of suspension drawn through the aperture ensures an accurate,

reproducible volume. Beckman Coulter counts and sizes individual particles at a rate of several thousand per second. This method is unaffected by particle shape, color, or density. The MAXM is a quantitative, automated, differential cell counter designed for in vitro diagnostic use. It measures these parameters in whole blood.

THE DATA WERE EXPRESSED AS MEAN ± STANDARD ERRORS OF MEANS (SEM). COMPARISONS AMONG DIFFERENT GROUPS WERE PERFORMED USING ANOVA. ALL TESTS WERE PERFORMED USING A TWO TAILED TESTS AT A SIGNIFICANCE LEVEL OF 0.05. SPSS – WINDOWS VERSION 16 – (SPSS. INC., CHICAGO, IL, USA) WAS USED FOR ALL STASTITISCAL ANALYSIS.

CHAPTER 4

RESULTS

4.1 Effect of Vitamin E on Sodium Arsenite-Induced Alterations in Haematological Parameters in Wistar rats

Parameters	Group A	Group B	Group C	Group D	Group 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]

Group A=Control, Group B=Vitamin E, Group C=Sodium Arsenite, Group D=Sodium Arsenite+Vitamin E (25mg/kg), Group E=Sodium Arsenite+Vitamin 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; $p < 0.05$.

CHAPTER 5

5.1 DISCUSSION

This study examined the protective effects of vitamin E against sodium arsenite–induced changes in hematological parameters in Wistar rats. The results clearly show that sodium arsenite has significant toxic effects on blood components, while vitamin E exhibits a dose-dependent protective effect across all measured hematological indices. These findings align with previous research identifying arsenic as a potent hematotoxic and oxidative stress–inducing toxicant, supporting the idea that antioxidants like vitamin E can reduce these harmful effects. Sodium arsenite (Group C) caused a notable decrease in red blood cell (RBC) count and hemoglobin (Hb) levels compared to the control group. This decrease indicates arsenite-induced anemia. Arsenic toxicity is known to impair erythropoiesis, interfere with hemoglobin synthesis, produce reactive oxygen species (ROS), and weaken cell membranes, leading to hemolysis. The sharp reduction in RBC and Hb observed in the arsenite-exposed rats agrees with findings from (Mondal *et al.,* 2016; Basher *et al.,* 2024; Ewere *et al.,* 2021), who reported that oxidative damage and bone marrow suppression are key mechanisms behind arsenic-related hematological problems. Vitamin E treatment, especially at 50 mg/kg (Group E), significantly improved RBC and Hb levels compared to Group C, confirming its protective antioxidant role. Vitamin E's ability to stabilize cell membranes and halt lipid peroxidation likely contributed to the improvement in these parameters. The dose-dependent enhancement also suggests that higher doses of vitamin E can offer greater protection to erythrocytes during oxidative stress. The significant elevation of white blood cells (WBCs) and neutrophils in the sodium arsenite group indicates inflammation and systemic immunological stress triggered by the toxicant. Sodium arsenite is known to activate inflammatory cytokines, stimulate neutrophil mobilization, and increase leukocyte

production as a defensive response to tissue injury. This observation is consistent with the findings of (Mashkoor *et al.,* 2023; Gholamine *et al.,* 2021), who demonstrated that arsenic exposure increases inflammatory markers due to oxidative tissue damage. Vitamin E co-administration significantly reduced WBC and neutrophil counts in both Groups D and E, showing that vitamin E helps modulate inflammatory responses by scavenging free radicals and reducing oxidative signals that trigger leukocytosis. The lower neutrophil levels in Group E further indicate a stronger anti-inflammatory effect at higher doses of vitamin E. In contrast to neutrophils, lymphocyte percentages were markedly reduced in the arsenite-only group. Lymphocyte reduction suggests immunosuppression, lymphoid tissue damage, or oxidative disruption of lymphocyte proliferation. Previous studies by (Basher *et al.,* 2024; Zubair *et al.,* 2020; Kaya and Şimşek 2024) corroborate this outcome, reporting that arsenic impairs immune competence and induces lymphocyte apoptosis. Vitamin E supplementation significantly restored lymphocyte counts, demonstrating that its antioxidant potential protects immune cells from oxidative destruction and supports recovery of immune regulatory functions. Again, the higher vitamin E dose showed greater restoration, reinforcing the dose-dependent trend. The neutrophil-to-lymphocyte ratio (NLR) is a sensitive indicator of systemic inflammation, oxidative stress, and immunological imbalance. The extremely elevated NLR observed in Group C clearly reflects severe physiological stress and inflammatory burden induced by sodium arsenite. The ability of vitamin E to lower NLR values in Groups D and E demonstrates its potent modulatory effect on both innate and adaptive immune components. Lower NLR in vitamin E–treated animals suggests reduced inflammatory intensity, restored immunological balance, and improved systemic resilience. Monocyte levels also exhibited significant changes across groups. Sodium arsenite caused a dramatic decline in monocyte percentage, indicating bone marrow suppression

or impaired monocyte mobilization. Monocytes play critical roles in phagocytic defense, inflammation regulation, and tissue repair; thus, their reduction aligns with arsenite-induced immunotoxicity. Vitamin E administration substantially improved monocyte levels in treated groups, with near-normal values achieved in Group E. These findings are consistent with studies by (Oyagbemi *et al.,* 2018; Satapathy *et al.,* 2021), demonstrating that vitamin E restores immune cell homeostasis during toxic exposure. Overall, the pattern observed in all hematological parameters confirms that sodium arsenite induces oxidative stress, inflammation, hematopoietic disruption, and immune suppression. Vitamin E, however, demonstrated strong protective effects across erythroid, myeloid, and lymphoid cell lines, indicating its broad-spectrum antioxidant ability. Its capacity to restore hematological integrity is likely due to its well-documented functions: scavenging lipid peroxyl radicals, protecting cell membranes, enhancing glutathione levels, reducing ROS formation, stabilizing erythrocyte membranes, and modulating inflammatory pathways. The superiority of the 50 mg/kg dose further emphasizes the importance of dosage in achieving maximal protection. This study therefore reinforces existing scientific evidence that vitamin E is a potent protective agent against arsenic-induced hematotoxicity. The results support the therapeutic potential of vitamin E as a supplemental antioxidant to mitigate the harmful effects of environmental toxicants, particularly in regions with high arsenic contamination. These findings may serve as a basis for future studies exploring combined antioxidant therapies, long-term supplementation, molecular mechanisms, or vitamin E interactions with other micronutrients in arsenic toxicity management.

5.2 CONCLUSION

This study showed that sodium arsenite causes significant hematological changes in Wistar rats, including decreased RBC and hemoglobin levels, increased WBC and neutrophil counts, notable lymphocyte reduction, higher neutrophil-to-lymphocyte ratio, and lower monocyte levels. These effects indicate anemia, inflammation, oxidative damage, and immune system imbalance due to arsenic toxicity. Vitamin E supplementation had a strong protective effect against these changes in a dose-dependent manner. Both 25 mg/kg and 50 mg/kg doses of vitamin E improved blood parameters, with the 50 mg/kg dose providing greater recovery. The protective effects of vitamin E are likely due to its powerful antioxidant properties, ability to stabilize cell membranes, anti-inflammatory effects, and capacity to modulate immune cell activity. Vitamin E effectively reduces sodium arsenite–induced blood toxicity and helps restore normal hematological function. This research offers strong evidence for the therapeutic potential of vitamin E in treating oxidative stress–linked blood disorders caused by arsenic exposure. It also suggests that dietary or supplemental antioxidants like vitamin E could be useful as preventive or supportive measures for those exposed to arsenic-contaminated environments.

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