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Co-administration of sodium selenite and sodium arsenite exacerbates hepatic, renal, pulmonary and splenic inflammation in rats

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ABSTRACT

This study examined the effect of co-administration of sodium selenite (SS) and sodium arsenite (SA) on inflammation in rats. Thirty (30) male Wistar rats were separated into 6 groups of five animals each. Group I (control) was given distilled water, groups II, III, IV and V were exposed to 20 and 40 ppm SA in drinking water, but in addition to that, groups IV and V only were co-exposed with 0.25 mg/kg bwt SS, while group VI was exposed to 0.25 mg/kg bwt SS only orally. Following 5 weeks of exposure, levels of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) were increased in SA-exposed groups. Synergistic and antagonistic effects were observed in co-exposed groups depending on dose and the specific tissue being considered. Synergism was observed in tissues co-exposed to higher dose (40 ppm) of SA + 0.25 mg/kgbwt SS except in the liver, where these markers were decreased compared with control. Level of IL-10 (anti-inflammatory marker) decreased in all the tissues investigated except in the lungs of animals co-exposed with 40 ppm SA. There was alteration in tissue architecture, revealing steatosis and hemorrhagic lesions as the common features in co-exposed groups. Results obtained indicate that the dose of SS used in this study may be toxic and not therapeutic against SA-induced tissue inflammation in rats.

Introduction

Arsenic (As) is an element that is ubiquitously available in the environment either as organic or inorganic form. The inorganic form exists in four different oxidation states: arsine (−3), elemental arsenic (0), arsenite (+3) and arsenate (+5)

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[1]. As a toxic metalloid, it is the 20th abundant element present in the earth crust and a major health distress for > 200 million people worldwide mainly due to the consumption of As-contaminated food and water [2].

Selenium (Se) also occurs as a natural metalloid, vital to human and other animal health in trace amounts but harmful when in excess [3]. It has four oxidation states which are: selenide (−2), elemental selenium (0), selenite (+4) and selenate (+6) [4]. As a vital component of antioxidant enzymes, it mediates many functions in human and animals [5]. It is found as an ingredient in many multivitamins and other dietary supplements for health benefit [3]. Several studies have demonstrated low levels of Se to be anti-carcinogenic. However, high Se can cause genotoxicity, induce carcinogenesis and cytotoxicity [1]. Se has also been reported to have one of the narrowest dose-range between dietary and deficiency [6]. The World Health Organization confirmed lower recommended Se intake of 34 and 26 μg day^{-1} for adult male and female respectively [7].

Arsenic, a well-established carcinogen has also been used to treat certain cancers by counter effects [8]. Several studies have demonstrated the interactions between arsenic and selenium [9]; also possible contradictions on the synergistic and antagonistic toxicity that exist between them which depend on the duration of exposure and extent of doses administered have also been indicated. Arsenic exists more as As V and As III states in aerobic and anaerobic conditions respectively [10]; however, their entrance in and metabolism in the cells differ [11]. Generally, metabolism of arsenic compounds depends on the state of cellular respiration and reactive oxygen species (ROS) production which can affect the arsenic speciation [12]. Selenite (Se IV) and selenate (Se VI) show different properties biochemically such that their energy consumption and toxicity during uptake and metabolism also differs [13]. Selenite is absorbed mainly into cells by passive diffusion, metabolized via different pathways to selenide (Se^{2-}) and subsequently used for biosynthetic processes [14].

Inflammation a response of cells to toxicants and infections can either be acute or chronic and has been implicated in several disease conditions [15]. Inflammatory markers such as TNF-α, IL-1β, IL-6, and IL-15 are mediators predominantly produced by T helper cells and macrophages which act on blood vessels and cells to stimulate inflammatory responses [16]. These responses thus produce reactive oxygen species (ROS) which subsequently damage the DNA of the cell and ultimately lead to tissue damage [16].

Once in the cell, both As and Se have been implicated in generation of ROS, development of chronic degenerative diseases and cardiovascular diseases associated with diabetes in humans [17]. These toxicants have also been shown to cause cytotoxicity and genotoxicity [18]. When As and Se are ingested, most of the species are carried to the liver where reduction to As III and Se IV respectively take place [1]. Literatures have also reported the antagonistic effect on co-exposure which was apparent by the formation of a less toxic As-Se complex selenobis (S-glutathionyl) arsinium ion $[(GS)_2AsSe]^-$ [19]. On the contrary, the synergistic effect of these toxicants has also been documented [20]. Owing to the complexity of the human system, the process of how Se interrelates with As metabolism is subject to multi-factors such as health status, nutritional status and dietary habits [1]. The therapeutic or toxic effect of a substance also depends on the dosage and extent of exposure hence; this study examined the effect of SS and SA co-exposure on pro-inflammatory and anti-inflammatory markers in liver, kidney, lung and spleen of male Wistar rats.

Materials and methods

Chemicals and kits

Sodium arsenite and sodium selenite that were utilized in this study were products of Sigma-Aldrich, Missouri, USA. Rats enzyme-linked immunosorbent assay (ELISA) (TNF-α, IL-1 β, IL-6 and IL-10) kits were all products of Cusabio Technology Llc, Houston, TX, USA. All other chemicals and reagents used were of investigative grade.

Experimental animals and treatments

Thirty male Wistar rats with an average body weight of 150 g were utilized for this study. Animals were accommodated in a room at ambient temperature (25 ± 2 °C) and a 12 h light–dark cycle (06:00–18:00 h). The guiding principles of the Institutional Animal Care and Use Committee were followed after being approved by the Animal Ethical Committee of the Department of Biochemistry, FUNAAB, Nigeria. Rats were acclimatized for two weeks and then divided into six groups of five each. Animals were then exposed to either arsenic (As) as SA, selenium (Se) as SS or co-exposed to both SA and SS. Group I is the control which received only distilled water, groups II and III were exposed to 20 and 40 ppm SA in drinking water, groups IV and V received in addition to 20 and 40 ppm SA respectively, 0.25 mg/kg bwt SS orally, while group VI was exposed to only 0.25 mg/kg bwt SS. The SS dose used in this study was as reported earlier by Aslanturk et al. [21].

At the end of 5 weeks exposure, the rats were anesthetized using phenobarbital (10 mg/kg bwt, intraperitoneally) and sacrificed. Liver, kidney, lungs and spleen were excised from which a section was cut and then fixed in phosphate-buffered formalin (10%) for histology. Another piece of the tissue was placed in ice-cold 0.1 M phosphate buffer (pH 7.4) from which 10% homogenate was obtained for estimations of inflammatory markers TNF- α, IL-1 β, IL-6, and IL-10.

Estimations of tissue IL-1 β, TNF- α, IL-6, and IL-10

Assessments were done according to the procedures described in the ELISA kits (Cusabio Technology Llc, Houston, TX, USA). Concisely, samples as well as standards were added into wells previously pre-coated with an antibody specific for IL-1

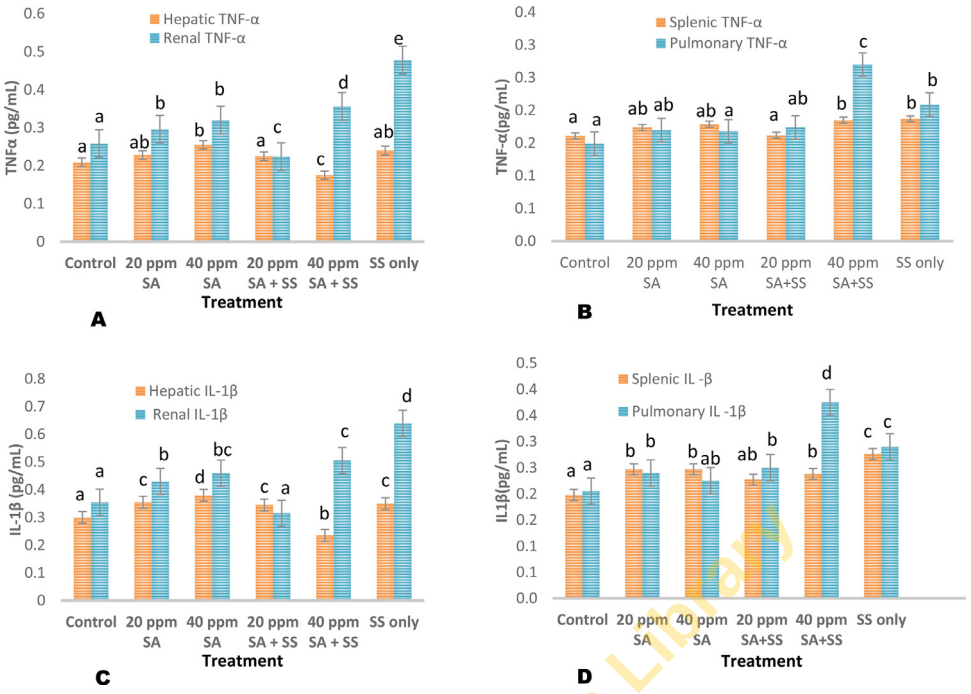

Fig. 1. A-D. Effect of SA and SS exposure on tissue TNF-α and IL-1β levels in rats. Values are mean ± S.E.M. of 5 rats. Bars labelled with different superscripts are significant statistically at $p < 0.05$. *A*= Hepatic and renal TNF-α levels; *B*= Splenic and pulmonary TNF-α levels; *C*= Hepatic and renal IL-1β levels; *D*= Splenic and pulmonary IL-1β levels.

β, TNF- α, IL-6, or IL-10. Afterwards, unbound materials were removed, and a biotin-conjugated antibody definite for each cytokine was added to the well. Avidin conjugated Horseradish Peroxidase (HRP) was then added to the wells after washing, followed by substrate solution to give a color proportional to the amount of IL-1 β, TNF- α, IL-6, or IL-10 bound in the initial step. Color change was stopped and the intensity of the color measured at 450 nm.

Histopathological analysis

Briefly, sections of tissues were fixed in 10% buffered formalin for 48 h. The tissues were further dehydrated in increasing concentrations of alcohol, cleaned twice in xylene with bench top tissue processor (Leica TP1020) and consequently fixed in paraffin with a tissue embedder (Leica EG1I50H). Afterwards, the embedded tissues were sectioned and stained with hematoxylin and eosin (H and E). Microanatomy of the stained tissues was observed under a light microscope and pictures taken with an attached digital camera (Leica Biosystems, UK). Histological assessment was done in a blinded fashion to avoid bias and finally obsereved under a Nikon light microscope

Statistical analysis

Data analysis was by one-way analysis of variance (ANOVA), then the least significant difference (LSD) was used to ascertain significant differences among the different groups by using Statistical Package for Social Sciences program version 20.0. Results were expressed as mean ± standard error of mean (S.E.M.) p values < 0.05 were considered to be statistically significant.

Results

Effect of treatments on tissue TNF-α and IL-1β levels

When compared with the control, there was a significant ($p < 0.05$) increase in hepatic TNF-α level in group exposed to 40 ppm SA while a decrease of 17% was observed in 40 ppm SA + SS co-exposed group. With the exception of 20 ppm SA + SS group, renal TNF-α increased in all exposed groups compared with the control (Fig. 1A). In the lungs and spleen, only in 40 ppm SA + SS and SS only groups were observed increases significant ($p < 0.05$) when compared with the control group (Fig. 1B). In hepatic tissue, IL-1β increased in all doses admisnistered with the exception of 40 ppm SA + SS group in which 22% decrease was observed. Similarly, renal IL-1β increased in all exposed groups but not in 20 ppm SA + SS animals (Fig. 1C). Splenic and pulmonary IL-1β levels also increased in exposed animals when compared with the control (Fig. 1D).

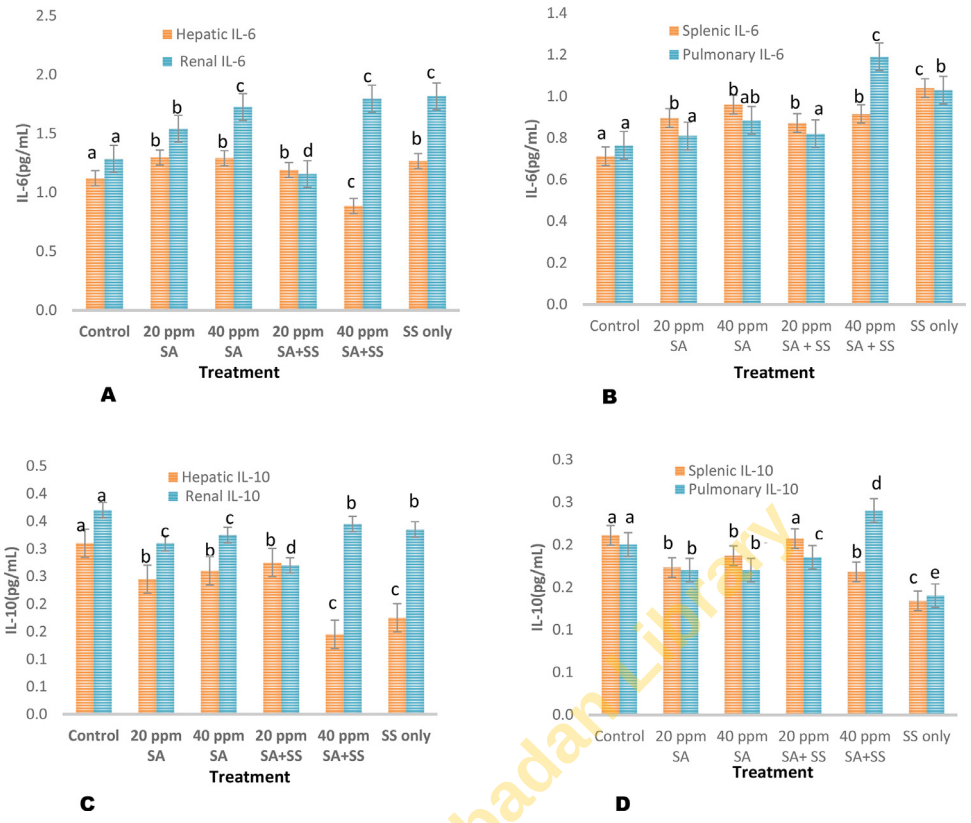

Fig. 2. A-D. Effect of SA and SS exposure on tissue IL-6 and IL-10 levels in rats. Values are mean ± S.E.M. of 5 rats. Bars labelled with different superscripts are significant statistically at $p < 0.05$. *A*= Hepatic and renal IL-6 levels; *B*= Splenic and pulmonary IL-6 levels; *C*= Hepatic and renal IL-10 levels; *D*= Splenic and pulmonary IL-10 levels.

Effect of treatments on tissue IL-6 and IL-10 levels

When compared with the control, hepatic IL-6 level increased significantly ($p < 0.05$) in all exposed groups except in 40 ppm SA + SS where an observed 18% decreased IL-6 level ensued (Fig. 2A). In the renal tissue, with the exception of 20 ppm SA + SS, IL-6 increased significantly in all exposed groups compared with the control (Fig. 2A). Furthermore, while splenic IL-6 level increased significantly at $p < 0.05$ in all exposed groups, pulmonary IL-6 increased significantly ($p < 0.05$) in 40 ppm SA + SS and SS only groups (Fig. 2B). Hepatic and renal IL-10 levels significantly ($p < 0.05$) decreased in SA, SS and SA + SS exposed animals when compared with control (Fig. 2C). Also, splenic IL-10 level decreased significantly when compared with control and 20 ppm SA + SS. Reduced level of pulmonary IL-10 in the same way hallmarked effect of treatments except in 40 ppm AS + SS (with 20% increase) (Fig. 2D).

Effect of treatments on liver histopathology

Liver histopathology is shown in Figs. 3A – F. Features revealed steatosis, moderate periportal infiltration and sinusoidal dilation in groups exposed to only SA (B and C). Hemorrhage with severe disseminated congestion involving the blood vessels and sinusoid, moderate microvesicular steatosis and periportal infiltration characterised D and E (SA + SS groups). Similarly, F (SS only) also revealed periportal infiltration, hemorrhagic lesions and congestion of the liver tissue.

Effect of treatments on kidney histopathology

Kidney histopathology is shown in Figs. 4A – F. Kidney histopathology revealed moderate disseminated and glomerular congestion in all exposed groups (B - F). In addition, multi-focal area infiltration of the glomerular cortex and hemorrhagic lesions were features observed in D and E (SA + SS) groups.

Effect of treatments on lung histopathology

Histopathology of lung of exposed rats are shown by Figs. 5A – F. Photomicrographs revealed disseminated alveolar hyperplasia and moderate to marked disseminated infiltration of the parenchyma by inflammatory cells. In addition, B (20 ppm

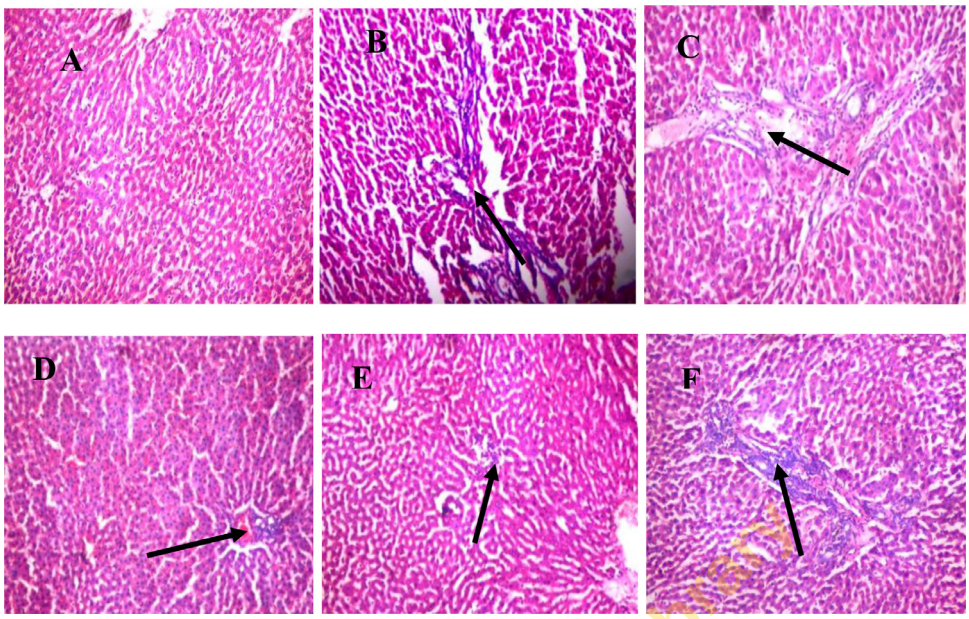

Fig. 3. A-F. Histopathological observations of liver stained with hematoxylin and eosin (H & *E* × 100) (*A* = Control group; *B* = 20 ppm SA; *C* = 40 ppm SA, *D* = 20 ppm SA + SS; *E* = 40 ppm SA + SS; *F* = SS only).

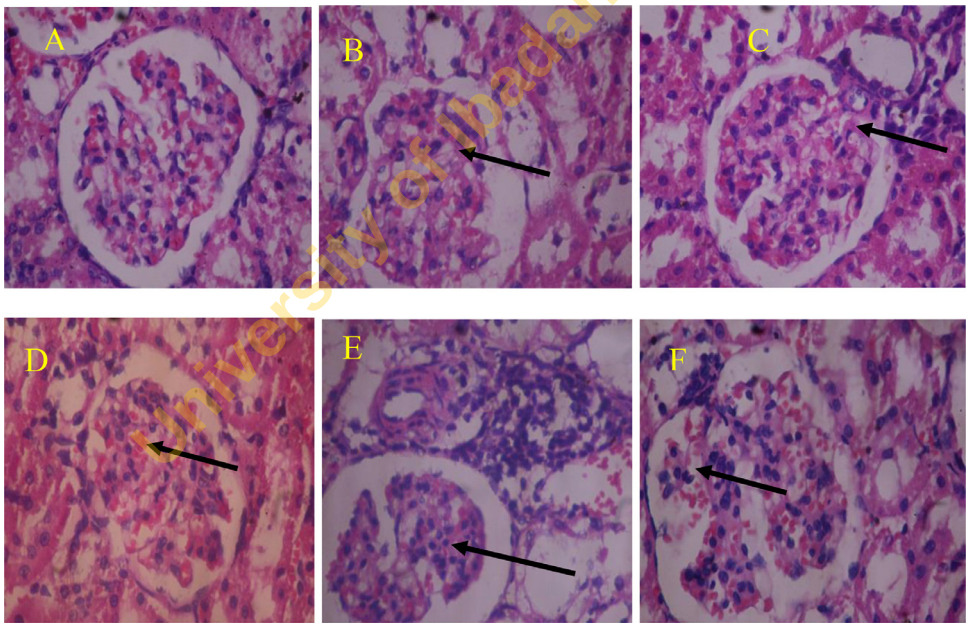

Fig. 4. A - F. Histopathological observations of kidney stained with hematoxylin and eosin (H & *E* × 400) (*A* = Control group; *B* = 20 ppm SA; *C* = 40 ppm SA; *D* = 20 ppm SA + SS; *E* = 40 ppm SA + SS; *F* = SS only).

SA) indicated marked to severe peri–bronchiolar infiltration while in C (40 ppm SA) infiltration of the parenchyma by inflammatory cells was observed. Disseminated hemorrhagic lesions characterized D and E while serious permeation of the parenchyma by inflammatory cells hallmarked lungs of animals exposed to SS only (F).

Effect of treatments on histopathology of the spleen

Figs. 6A – F indicate histology of the spleen. Photomicrograph of Fig. A (control) indicates a well delineated white and red pulp. Figs. B – F revealed few megakaryocytes trabecular artery. In addition, Fig. B (20 ppm SA) featured focal area of

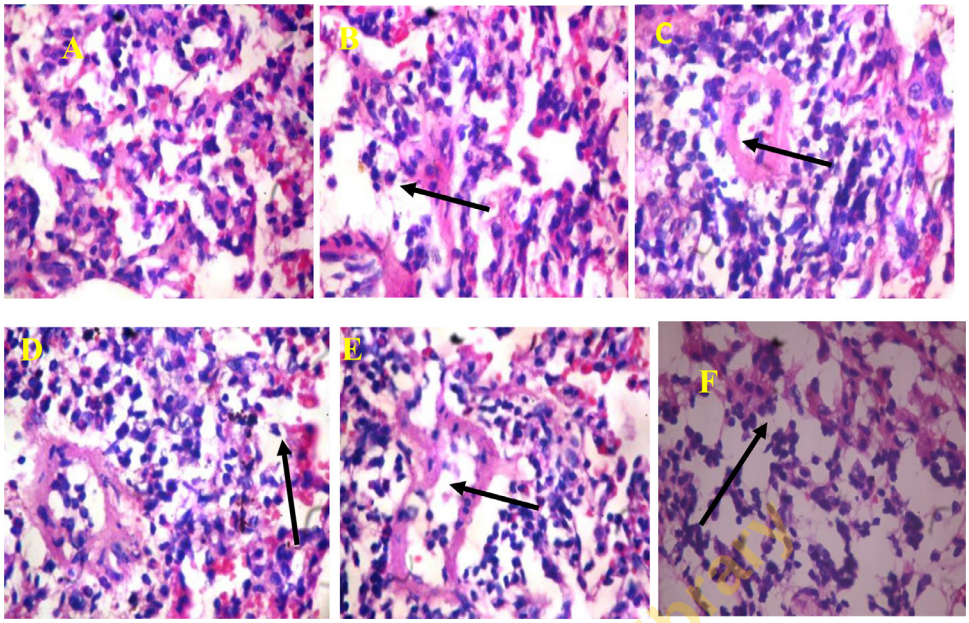

Fig. 5. A-F. Histopathological observations of lungs stained with hematoxylin and eosin (H & $E \times 400$) (A = Control group; B = 20 ppm SA; C = 40 ppm SA, D = 20 ppm SA + SS; E = 40 ppm SA + SS; F = SS only).

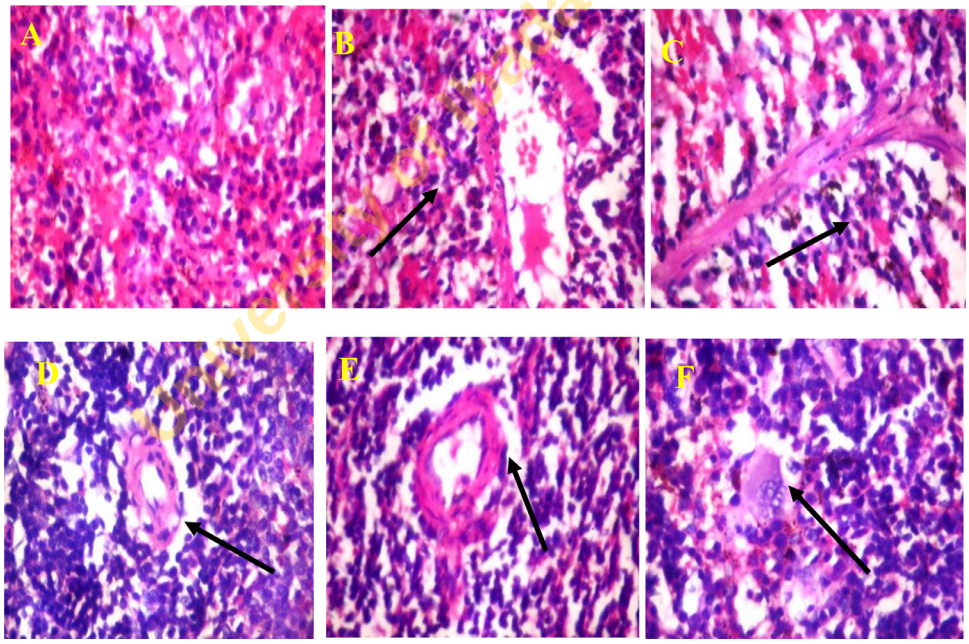

Fig. 6. A-F. Histopathological observations of spleen stained with hematoxylin and eosin (H & $E \times 400$) A = Control group; B = 20 ppm SA; C = 40 ppm SA, D = 20 ppm SA + SS; E = 40 ppm SA + SS; F = SS only.

fibrosis, while C (40 ppm SA) showed both focal area of fibrosis and moderate to severe disorganized white pulp. However, overall feature of the splenic tissue showed no significant lesion in exposed groups.

Discussion

Inflammation is part of the body's response to injury and harmful stimuli like pathogen, irritants or damaged cells which then leads to production of mediators such as inflammatory cytokines (markers)- biological messengers that act on cells to

produce inflammatory response for host defense [22]. In this study, levels of inflammatory cytokines- TNF-α, IL-1β, IL-6 and IL-10 in the tissues were affected by exposure to SA and SS. The observed alterations were tissue specific. TNF-α, IL-1β and IL-6 are pro-inflammatory markers that participate in production of acute phase proteins [23]. TNF-α, an essential mediator of acute inflammation, promotes acute phase proteins production [24], IL-1β which is a potent pro-inflammatory cytokine vital for host-defense response to injury and infection [25], while IL-6 acts both as a pro-inflammatory cytokine and an anti-inflammatory myokine by inhibiting the effects of IL-1 and TNF-α while activating IL-10 in humans. IL-10 is a potent anti-inflammatory cytokine with properties involved in limting host immune response thereby preventing damage to the host and maintaining normal tissue homeostasis [26].

In this study, there was increased levels of pro-inflammatory markers (TNF-α, IL-1β and IL-6) in groups exposed to SA and SS. Metabolism of SA and SS have been linked to production of ROS [27]. Increased ROS has been indicted in triggering inflammatory response since oxidative stress and inflammation are linked in a complex feedback cycle such that ROS trigger transcription factors that upregulate expressions of pro-inflammatory cytokines as reported by Das et al. [28] Similarly, ROS have been implicated in oxidative stress and malfunctioning of different tissues including liver, lungs, kidney and spleen so that the extent of damage caused were attributed to either overproduction or an ineffective elimination process of the ROS generated [29]. Aside this, SA and SS are toxicants foreign to the body and trigger immune responses once introduced into the biological system and one of such responses is increased level of cytokines which can lead to generation of more ROS and mutagenesis, thereby, contributing to pathogenesis of diseases caused by the toxcants [30]. Increased level of pro-inflammatory markers also hallmarked tissues of animals co-administered SA and SS, however decreased level of these cytokines ensued in the liver of animals co-exposed to 40 ppm SA and SS. Depending on the doses administered, selenium (Se) has been reported to antagonize arsenic (As) toxicty thereby alleviating its effect either by the formation of an As–Se compound- selenobis (S-glutathionyl) arsinium ion $[(GS)_2AsSe]^-$, which causes less damage on cells [19] or by up-regulation of seleno-proteins such as glutathione peroxidase and thioredoxin reductase thereby preventing As-induced oxidative damage [31]. On the contrary, some literatures have reported that Se enhances the toxicty of As by mutually inhibiting the formation of each other's methylated metabolites thus resulting in retention of more inorganic As and/or Se in tissues thereby producing a synergistic effect [1]. Another factor which is the availability of glutathione (GSH) and S-adenosyl methionine (SAM) required for detoxification of both As and Se. GSH is a reductant while SAM is the methyl group donor; limited levels of these metabolites thus lead to retention of inorganic As and Se in the body [32] ultimately leading to a concerted toxic effect. From our results we propose observed increased level of these biomarkers implies synergistic effect between the two toxicants while decreased level suggests antagonism. Sodium selenite had an "addition effect" with 40 ppm SA in all the tissues except in the liver where antagonism (decreased cytokines) was observed. This decrease might have resulted because of high intracellular concentration of GSH in the liver which is important for the conversion of $As(OH)_3$ to $(GS)_2AsOH$ by the substitution of –OH group by glutathionyl moieties while Se IV spontaneously reacts with GSH to form hydrogen selenide (H_2Se) [13]. By nucleophilic attack of HSe^-on $(GS)_2AsOH$, $(GS)_2AsSe^-$ is formed; it is then transformed to $[(CH_3)_2As(Se)_2]^-$ and ultimately excreted out of the cell thus reducing the concentration of the toxicant available [33]. Furthermore, early work by Moxon and DuBois [34] reported the amelioration of Se-induced hepatic damage when 5 mg/kg of As III was administered orally. However, information from Sah et al. [35] revealed Se concentration between 0.3 - 0.6 mg/kg in diets improved antioxidant capacity and immunity of rats to counter As toxicity. Effects of these two substances have similarly been shown to be dose-dependent [36]. From our results, the 40 ppm dose and 0.25 mg SS combination alleviated possible inflammation in the liver but not in other tissues studied. On the contrary, anti-inflammatory cytokine (IL-10) was lowered in all tissues studied except in the pulmonary tissue of rats co-exposed to 40 ppm SA and SS. This is an indication that co-exposure of SA and SS does not have any anti-inflammatory effect in the inflamed tissues.

In this current investigation, several pathological changes were observed in tissues of exposed rats. Steatosis, moderate periportal infiltration and sinusoidal dilation characterized the liver of rats exposed to SA while hemorrhage with severe disseminated congestion and periportal infiltration characterized the co-exposed animals. Reports by Al-Forkan et al. [37] implicated sinusoidal dilation to be found primarily in hepatic tumors thus we suggest possible tumor cells in exposed animals. While multi-focal area infiltration of the glomerular cortex with mononuclear cells epitomized the renal tissue, permeation of the parenchyma by inflammatory cells characterized the pulmonary tissue. In addition, disseminated hemorrhagic lesion featured in the lungs of co-exposed animals. Considering the spleen, there was focal area fibrosis although; overall architecture of this tissue was not altered. Steatosis evident in the tissues might have resulted from deposition of fat droplets owing to altered lipid metabolism which has been reported earlier by Afolabi et al. [38]. Reports from literatures have shown As to cause hepatocellular swelling and necrotic features characterizing the kidney [39]. In addition, enlargement of the white pulp was observed in the spleen [37]. In agreement, Al-Forkan et al. [37] also reported features such as edema, necrosis and presence of inflamed cells in sections of rat liver exposed to As III. Furthermore, inflammatory cells and enlargement of the white pulp characterized the renal and splenic tissues respectively [37]. From this study, we suggest the altered architectural make-up of tissues studied as a possible factor that can induce formation of cancer cells which is characteristic of As toxicity. To also mention that the SS dose (0.25 mg/kg bwt) when administered alone was not therapeutic owing to the histopathological influence observed on the various tissues studied. From our results, we hereby conclude that depending on the dose administered, co-administration of sodium arsenite and sodium selenite can alter tissue architecture and similarly stimulate inflammation by the up-regulation of pro-inflammatory cytokines.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Olubisi E. Adeyi: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Project administration. **David O. Babayemi:** Methodology, Investigation, Supervision. **Babajide O. Ajayi:** Methodology, Investigation, Resources, Project administration. **Akindele O. Adeyi:** Resources, Writing - review & editing. **Ayomide H. Ayodeji:** Methodology, Investigation, Resources, Project administration. **Adenike O. Oguntayo:** Methodology, Investigation, Resources, Project administration. **Adenike T. Adeyemi:** Methodology, Investigation, Resources, Project administration. **Oluwatoyin E. Olaiyapo:** Methodology, Investigation, Resources, Project administration. **Shukurat T. Adeoye:** Methodology, Investigation, Resources, Project administration.

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