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Ethanol extract of *Vitellaria paradoxa* (Gaertn, F) leaves protects against sodium arsenite - induced toxicity in male wistar rats

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ABSTRACT

The inadvertent exposure to arsenic has been associated with diverse diseases such as cancers. *Vitellaria paradoxa* is a medicinal plant with antidiabetic and antiproliferative properties. Here, we assessed the ameliorative role of Ethanol Leaf extract of *Vitellaria paradoxa* (ELVp) in Sodium Arsenite (SA) - induced toxicity in rats after oral treatment for two weeks as follows: Group 1 (Control, distilled water), Group 2 (Vitamin E, 100 mg/kg), Groups 3 and 4 (ELVp, 100 & 200 mg/kg respectively), Group 5 (SA, 2.5 mg/kg), Group 6 (SA + Vit E) and Group 7 (SA + ELVp (100 mg/kg) and Group 8 (SA + ELVp (200 mg/kg). The results indicated that SA significantly increased liver and kidney function markers and elevated platelet, white blood cell (WBC) count and malondialdehyde levels in rats. Additionally, SA decreased Red Blood Cell (RBC), Hemoglobin (HGB) and Hematocrit (HCT) levels in rats ($p < 0.05$). Sodium arsenite caused mild expression of BCL-2 protein> NF-Kb = p53 in the kidney of rats. However, ELVp ameliorated SA-induced toxicity in the liver and kidney of rats with respect to these markers. Overall, ELVp has hepatoprotective, nephroprotective and apoptotic properties against sodium arsenite-induced toxicity.

1. Introduction

Exposure to arsenic, an environmental toxicant, has been related to some human diseases such as cancer [1,2]. Arsenic, existing in the inorganic and organic forms is ubiquitous in the ecosystem [3]. The major route of arsenic contact is via intake of polluted water and dietary ingestion of contaminated food [4,5]. This metalloid have shown toxicity to the lungs [6], kidney [7], intestine [8], spleen, heart [9], blood cells [9,10], hepatocytes [11–13], and immune cells [3] *in vivo*.

The destructive outcome of arsenic on diverse tissues and organs can be deduced from its metabolism via enzymatic methylation and reduction reactions. The major bioactive metabolites from these reactions are dimethylarsinic acid (DMA^{V}) and dimethylarsinous acid DMA^{III} [14]. Although the liver and intestines are the organs responsible for arsenic metabolism, the metabolites extensively interact with blood and other tissues [1]. Cellular and molecular studies have revealed that arsenic exposure produces reactive oxygen species via its cellular oxidation – reduction reaction [15]. This will ultimately lead to cellular oxidative stress [16–18].

One key aspect, pointed out in literature for combating ill health situation arising from arsenic toxicity is the application of antioxidants such as vitamins C and E [19,20]. Recently, diverse medicinal plants are now being evaluated for possible presence of promising phytochemicals with therapeutic property [21–23].

Vitellaria paradoxa (Gaertn. F) is commonly called Shea butter tree because the oil from the seeds is used to produce shea butter cream. It is known locally in Nigeria among different ethnic groups as 'Emi' (Yoruba), 'Okwuma' (Igbo) and 'Kadaya' (Hausa) [24]. It belongs to the Sapotaceae family and genus Vitellaria, and indigenous to Africa. In Nigeria, it is abundantly found near towns and villages in the savannah zones. *V. paradoxa* plant parts; root, stem bark, leaves, seeds and fruits have been used for treating diarrhea, dysentery, helminths and the gastrointestinal infections [25]. The bark is used for cough suppression and leprosy treatment [26]. Furthermore, antifungal [27], antibacterial [28], antidiabetic [29], anti-inflammatory/anti-arthritic [30] and anti-proliferative [31] activities have been reported.

Presently, information on the ameliorative effects of *Vitellaria paradoxa* on sodium arsenite-induced toxicity is scarce in the literature. Hence, we hypothesize that *Vitellaria paradoxa* leaf extract (ELVp) would suppress or protect against sodium arsenite-induced hepatotoxicity and nephrotoxicity in rats. Therefore, the purpose of this study was to evaluate the ameliorative role of ethanol extract of *Vitellaria paradoxa*

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(Gaertn.F) leaves in sodium arsenite-induced toxicity in the liver and kidney of male Wistar rats.

2. Materials and methods

2.1. Chemical and kits

Sodium arsenite ($NaAsO_2$; BDH chemicals Ltd poole England) dosage (1/10th of the oral LD_{50}) was administered according to [32]. Also, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphates (ALP), urea and creatinine kits were procured from Randox Laboratories, Crumlin, UK.

2.2. Ethical and institution approval

The study was approved by the Animal Care, Use and Research Ethic Committee (ACUREC) of the University of Ibadan prior to commencement of experiment (Reference: UI-ACUREC 16/0019).

2.3. Preparation of leaves extract of Vitellaria paradoxa (ELVp)

Fresh leaves of *V. paradoxa* were obtained from Saki, North of Oyo State, Nigeria. They were identified, proven authentic and deposited at the herbarium of the Department of Botany, University of Ibadan, Nigeria. (Voucher No: UIH-22624).

V. paradoxa leaves were cleaned under running tap water, drained and air-dried at room temperature in the Department of Biochemistry, University of Ibadan. Dried, crispy leaves were milled into powdery form.

Exactly 500 g of the powdered sample was soaked at room temperature in ethanol (70 %) for 72 h. The mixture was filtered and at 40 ℃ using a rotary evaporator . The concentrate was then kept at 4 ℃, until needed. The percentage yield for ethanol leaves extract of *Vitellaria paradoxa* was 28.53 ± 2.171 %.

2.4. Experimental animal's maintenance and treatment

Forty male Wistar albino rats (100−120 g) were acquired and housed at Animal House Facility, Department of Biochemistry, University of Ibadan and fed with rats' pellets from Ladokun Feeds, Mokola, Ibadan, Nigeria and water *ad libitum*. Animals were acclimatized for 7 days and maintained at 12 h light/12 h dark cycle throughout the period of study. Worthy of note, the doses chosen for this study were selected after a preliminary lethal dose study was carried out, in which the LD_{50} was observed to be above 5000 mg/kg. In addition, animals were randomly divided into eight groups of five animals each; Control (distilled water), Vitamin E (100 mg/kg), ELVp (100 & 200 mg/kg respectively), SA (2.5 mg/kg), SA + Vit E, SA + ELVp (100 & 200 mg/kg respectively). In previous studies, acute toxicity study with SA was on alternate days for four weeks. Hence, in this study, we chose two weeks of daily exposure to understand the ameliorative effects of ELVp on SA-induced toxicity in rats.

2.5. Collection of blood and harvesting of tissues

Two hours prior to animal sacrifice, 0.04 % colchicine was administered at (10 mL/kg body weight). Blood samples were collected into EDTA and plain bottles through retro-orbital bleeding. The blood samples in the plain bottles were allowed to clot. Thereafter, they were centrifuged for 30 min at 3000 *g*, serum was transferred into clean sterile sample bottles and stored at -20 ℃ until needed. The blood samples in the EDTA heparinized bottles were used for hematological assays.

Animals were thereafter sacrificed by cervical dislocation. The liver and kidney were carefully excised and blotted with filter paper to remove traces of blood and perfused with KCl solution (1.15 %). The excised liver and kidney samples were fixed in neutral buffered formalin (10 %) and processed at the Pathology Department, University College Teaching Hospital (UCH), Ibadan for histological viewing under light microscope after paraffin sectioning and staining using Haematoxylin-Eosin dye.

2.5.1. Measurement of percentage change in body weight, relative liver and kidney weights

The initial weights of the rats were measured after acclimatization before treatment was administered. Also, after the last day of treatment, before sacrificing the animals, the final weight for each animal was measured. Therefore, percentage change in body weight was calculated with the formula below.

$$\%\ \text{change in body weight} = \frac{\text{Final weight of animal– initial weight of animal}}{\text{Initial weight of animal}} \times 100$$

The relative liver and kidney weights, were calculated as shown below.

$$\text{Relative organ weight} = \frac{\text{Weight of the organ}}{\text{Final body weight}} \times 100$$

2.6. Biochemical assays

Serum activities of Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), creatinine and urea were measured spectrophotometrically (UV/VIS spectrophotometer 752S) using commercial kit (Randox, UK) following the manufacturer's protocol. Also, differential white blood cell counts, red blood cells estimation, hemoglobin and hematocrit level determination, lymphocytes and platelets counts were carried out on a 3- part differential hematology auto-analyzer, England. Furthermore, according to the method of Varshney et al. [33], Lipid peroxidation (LPO) was determined in the supernatant of liver homogenized samples and MDA level was calculated based on the method of Adám-Vizi and Seregi [34].

2.7. Immunohistochemical determination of NF-Kb, p53 and BCL-2

The paraffin embedded tissues were placed on charged slides and then de-paraffinized by immersing 5 min in xylene (twice). Next was rehydration in 100 % of ethanol for 3 min (twice), in 95 % 3 min (twice) and in 70 % for 3 min (once). Thereafter, rinsing with wash buffer for 5 min (twice). The retrieval of antigen was done to expose the antigen epitope by incubating for 10−20 min using 10 mM citrate buffer pH 6.0 which has been preheated and allowed to cool. It was then rinsed with wash buffer. Blocking buffer (10 % FBS in PBS) was applied to the sections and incubated for 15 min in a humidified chamber at room temperature. Thereafter, slides were removed and rinsed with wash buffer. Next, application of primary antibody after dilution (130 µL) to sections and subjection to an hour incubation. Slides were properly washed using wash buffer, the secondary antibody (130 µL, diluted biotinylated + streptavide HRP) was applied to the sections with 30 min incubation process at room temperature and then washed buffer was used to rinsed slides for a few minute. Then, the slides were incubated with Sev-HRP conjugate for 15 min and rinsed with washed buffer for 5 min (twice). After this, using DAB substrate solution (130 µL) and hematoxylin sessions were stained and counter stained. They were properly rinsed under running tap after each application. After this, it undergoes dehydration by transferring to alcohol (95 %, 95 %, 100 %, 100 %) for 5 min each. The slides were transferred to xylene for 5 min (thrice) and thereafter covered with coverslip using mounting solution. Lastly, with the help on an optical light microscope, slides were observed at X400 magnification.

2.8. Statistical analysis

All data are presented as mean ± standard deviation. Differences among groups were evaluated using One-way analysis of Variance (ANOVA), using Graph pad Prism 6.0 with p values < 0.05 considered statistically significant.

3. Results

3.1. Effects of ethanol leave extract of V. paradoxa (ELVp), Vit E and SA on body and organ weights of rats

We recorded body and organ weights of animals since increase or decrease in body / organ weight is an indication of the total wellbeing of animals. Fig. 1 shows the effects of ELVp or Vitamin E on the percentage change in body and relative organ weights of sodium arsenite – treated Wistar rats. The difference between initial body and final body weights of the animals were used to evaluate the percentage body weight change (Fig. 1A). While relative liver and kidney weights were determined from weight of harvested liver and kidney tissues (Fig. 1B and C).

Although, SA had no significant effect on percentage body weight and relative liver weight however, SA resulted in significant reduction in relative kidney weights when compared with the control ($p < 0.05$). Vitamin E, ELVp (100 and 200 (mg/kg)) also elevated percentage change in body weight and relative liver weight significantly ($p < 0.05$) when compared with control. Furthermore, when SA was co-treated with the extracts, it was noticed that 100 mg/kg of ELVp significantly increased the weight of relative kidney weights when compared with SA alone.

3.2. Effect of ELVp on SA- induced hepatotoxicity

We sought to understand the ameliorative role of ELVp in SA-induced hepatotoxicity by carrying out selected liver function markers (AST, ALT and ALP). Hence, Figs. 2 and 3 show the effects of ELVp and Vit E on SA-induced hepatotoxicity after treatment for two weeks. The activities of liver markers ALT and ALP increased in SA-treated rats in comparison with control ($p < 0.05$). While, Vitamin E caused significant decrease in AST and ALP activities in comparison to control ($p < 0.05$). Similarly, co-treatment groups administered SA + Vitamin E or SA + ELVp (100 mg/kg) had significant decreases in AST, ALT and ALP activities compared with SA treated rats (Fig. 2A–C). The histology of the liver supports this finding (Fig. 3). From the photomicrograph of the histology Fig. 3A, B and D, ELVp 200 (mg/kg) showed no significant lesion. While Fig. 3C (ELVp 100 mg/kg) revealed mild vascular congestion. Fig. 3E (SA only) showed periportal inflammation, moderate ductular reaction and fibroblast proliferation in the portal triad. However Fig. 3F–H (which are the co-administered groups) ameliorated the inflammation mildly.

3.3. Effects of ELVp on SA- induced nephrotoxicity

We assessed the effects of ELVp or Vit E respectively on SA-induced renal toxicity (Figs. 4 and 5). Both creatinine and urea were used as markers for renal toxicity because both are by-products of renal excretion. The concentration of creatinine in SA-treated rats increased significantly with p value < 0.05 when compared with the control. However, co-administration of vitamin E or ELVp ameliorated SA-induced elevation of creatinine in rats (Fig. 4A). Furthermore, we observed that SA elevated urea concentration significantly (having p value of 0.0029) when compared to control. However, Vitamin E and ELVp 100 mg/kg extract respectively significantly decreased ($p < 0.05$) urea concentration when compared to SA-treated rats. Similarly, ELVp + SA significantly reduced the concentration of urea (Fig. 4B, $p < 0.05$).

The histology of the kidney revealed the nephroprotective action of ELVP and Vitamin E on sodium arsenite-induced nephrotoxicity (Fig. 5). We observed no significant lesion for Fig. 5A–D (Control, Vitamin E alone, ELVp 100 and 200 mg/kg respectively). While Fig. 5E (SA alone) showed moderate glomerular capillary and interstitial congestion and peritubular inflammation. Also, Fig. 5F & G (SA and vit E or ELVp 100 mg/kg co-treatment) showed mild hemorrhagic lesion and moderate peritubular inflammation respectively. Lastly, we observed no significant lesion in SA + ELVp 200 mg/kg co-treated group (Fig. 5H).

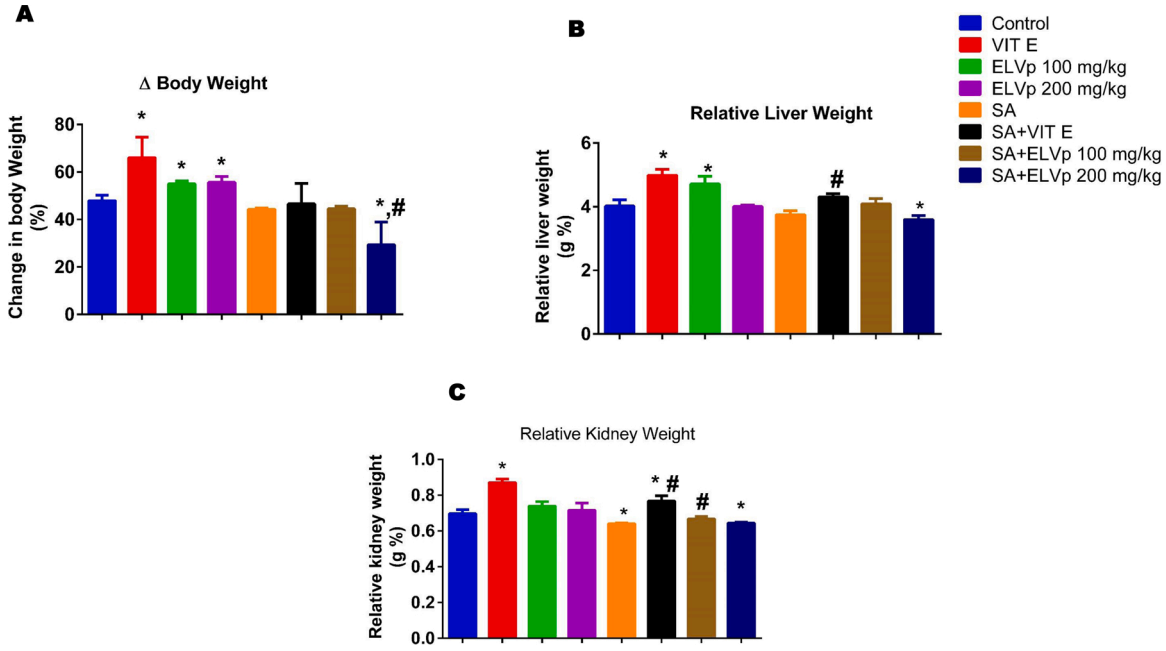


Fig. 1. Effects of ELVp & Vit E on body and organ weights of SA-induced male Wistar rats. Change in % body weight (A); relative liver weight (B); and relative kidney weight (C) of male Wistar rats exposed to ELVp, vitamin E and sodium arsenite for 14 days. Data are presented as Mean ± SD of 5 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p < 0.05$).

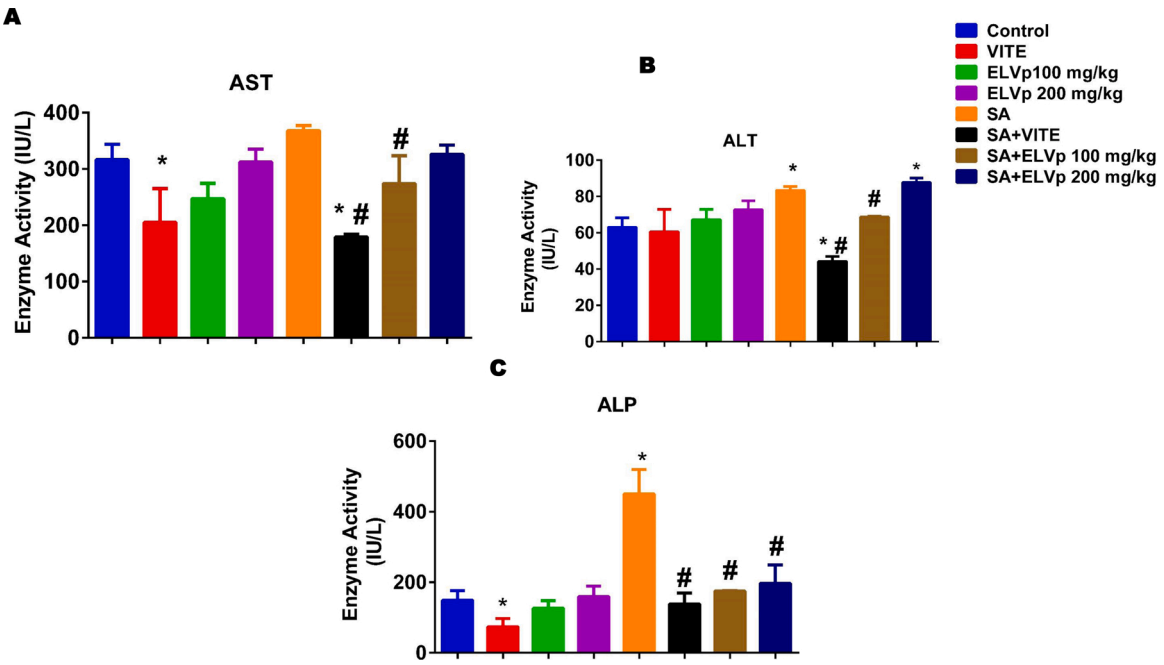


Fig. 2. The effects of ELVp on sodium arsenite-induced hepatotoxicity on male Wistar rats. Aspartate transferase (AST) enzyme activity (A); Alanine transferase (ALT) enzyme activity (B); and Alkaline phosphatase (ALP) enzyme activity (C) of male Wistar rats exposed to ELVp, vitamin E and sodium arsenite for 14 days. Data are presented as Mean ± SD of 5 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p< 0.05$). The unit for the enzyme activity is international unit per liter (IU/L).

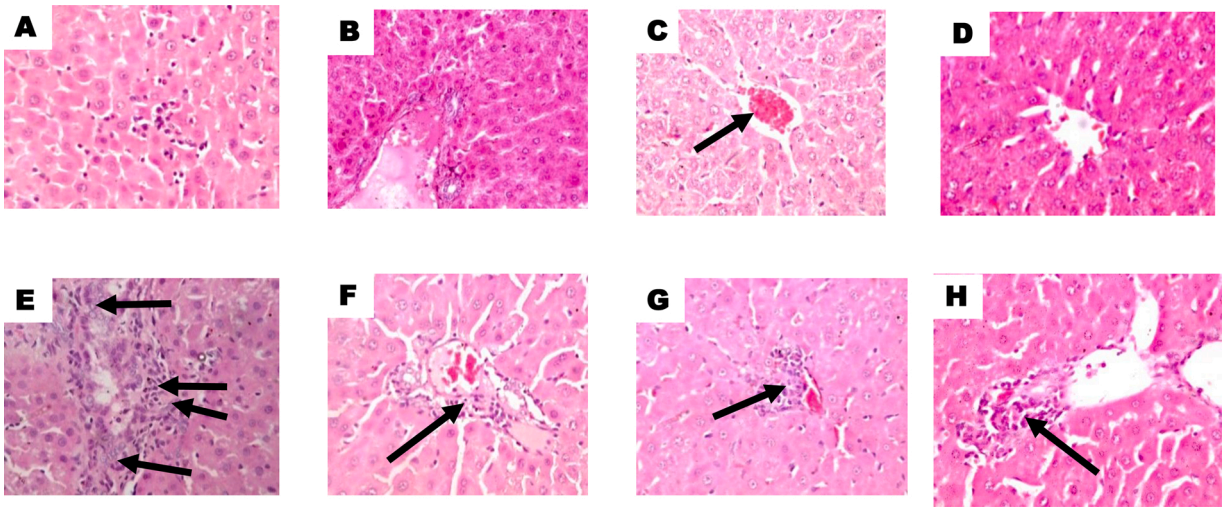


Fig. 3. Photomicrographs showing effects of ELVp on the liver of rats exposed to sodium arsenite (2.5 mg/kg.bw) (× 400 magnification). Where A is control: No significant lesion. B is VIT E: No significant lesion. C is ELVp 100 mg/kg: Mild vascular congestion. D is ELVp200 mg/kg: No visible lesion. E is SA: mild periportal inflammation (black arrow), mild increase in the connective tissue (dashed arrow) and vesicular nuclei (thin arrow) of some cells in the portal triad. F is SA + Vit E: Mild periportal inflammation. G is SA + ELVp100 mg/kg: Mild periportal inflammation and mild vascular congestion. H is SA + ELVp 200 mg/kg: mild periportal inflammation.

3.4. Effects of ELVp on haematological parameters of rats treated with sodium arsenite

The effects of ELVp on haematological parameter are depicted in Tables 1 & 2 . Sodium arsenite (SA) alone significantly decreased red blood cell count, haemoglobin and hematocrit levels in comparison to the control group as shown in Table 1 ($P < 0.05$). However, co-administration of sodium arsenite (SA) with ELVp 200 mg/kg significantly increased the red blood cell count and haemoglobin levels when compared to SA ($p < 0.05$). Furthermore, Table 2 shows that treatment of male Wistar rats with SA significantly increased platelet, lymphocyte and white blood cell count when compared with the control group ($p < 0.05$). However, ELVp 200 mg/kg reduced SA-elevated platelet and lymphocyte counts when rats were concurrently exposed to SA and ELVp ($p < 0.05$).

3.5. Effects of ELVp on liver lipid peroxidation of rats treated with sodium arsenite

The concentration of liver MDA increased notably in SA-treated rats as against control (Fig. 6, $p < 0.05$). However, rats dosed with Vitamin E and ELVp (100 mg/kg) revealed a notable decrease in MDA level ($p <$

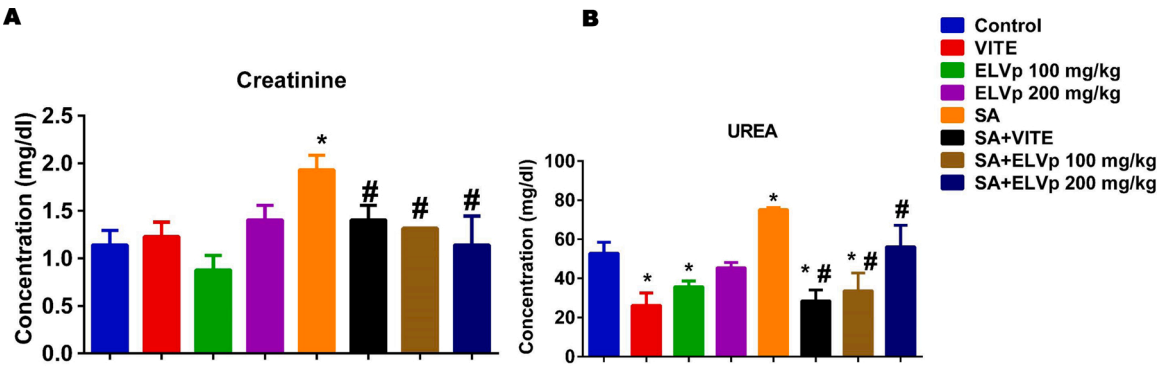


Fig. 4. The effects of ELVp on sodium arsenite- induced nephrotoxicity on male Wistar rats. Creatinine concentration (A) and Urea concentration (B) of male Wistar rats exposed to ELVp, vitamin E and sodium arsenite for 14 days. Data are presented as Mean ± SD of 5 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p< 0.05$).

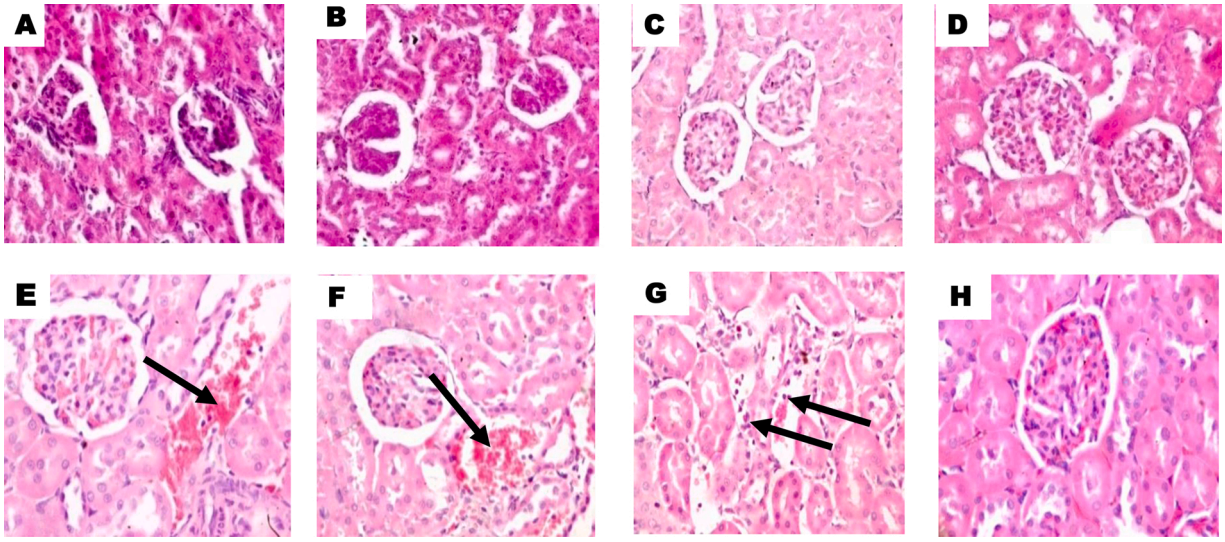


Fig. 5. Photomicrographs showing the effects of ELVp on the kidney of rats exposed to sodium arsenite (2.5 mg/kg b.w) (× 400 magnification). Where A is control: No significant lesion. B is VIT E: No significant lesion. C is ELVp 100 mg/kg: No significant lesion. D is ELVp200 mg/kg: No significant lesion. E is SA: mild hemorrhagic lesion (black arrow) and peritubular inflammation. F is SA + Vit E: slight hemorrhagic lesion (black arrow) and slight peritubular inflammation (thin arrow). G is SA + ELVp100 mg/kg: moderate peritubular inflammation (thin arrow). H is SA + ELVp 200 mg/kg: No significant lesion.

Table 1
Effects of ELVP on RBC, HGB & HCT PARAMETERS of rats treated with sodium arsenite.

GROUPS	RBC	HGB	HCT
Control	7.04 ± 0.255	152.0 ± 6.000	48.08 ± 0.909
Vit E 100 mg/ kg	6.42 ± 0.248*	136.3 ± 2.887*	37.00 ± 0.318*
ELVp 100 mg/ kg	6.57 ± 0.066	134.7 ± 3.512*	43.17 ± 1.775*
ELVp 200 mg/ kg	6.84 ± 0.200	150.0 ± 4.359	48.24 ± 0.912
SA 2.5 mg/ kg	6.40 ± 0.394*	133.3 ± 2.517*	41.77 ± 0.923 *
SA + Vit E	6.00 ± 0.046*	142.7 ± 5.686	41.24 ± 1.406 *
SA + ELVp 100 mg/kg	6.84 ± 0.129	136.7 ± 6.351*	41.79 ± 1.561 *
SA + ELVp 200 mg/kg	7.29 ± 0.358 #	149.7 ± 1.528 #	44.16 ± 1.444*

Data are presented as Mean ± SD of 5 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p< 0.05$).
Where RBC is Red blood cell; HGB is Hemoglobin; and HCT is Hematocrit.

Table 2
Effects of ELVP on Platelet, lymphocyte and white blood cell parameter of rats treated with sodium arsenite.

GROUPS	PLT	LYMP	WBC
Control	629.3 ± 60.960	81.50 ± 4.067	4.97 ± 0.808
Vit E 100 mg/kg	560.7 ± 22.550	79.67 ± 4.186	6.93 ± 1.387 *
ELVp 100 mg/kg	683.0 ± 30.450	89.05 ± 0.511 *	6.60 ± 0.964 *
ELVp 200 mg/kg	566.7 ± 22.230	89.33 ± 1.819 *	5.600 ± 0.520
SA 2.5 mg/kg	738.0 ± 51.880*	90.08 ± 4.233 *	6.733 ± 0.777*
SA + Vit E	634.7 ± 25.580#	75.58 ± 2.970 *,#	4.40 ± 0.265 #
SA + ELVp 100 mg/ kg	676.0 ± 65.280	90.73 ± 0.233 *	7.23 ± 1.960
SA + ELVp 200 mg/ kg	655.0 ± 37.320	72.74 ± 2.067 *,#	8.27 ± 1.050

Data are presented as Mean ± SD of 5 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p< 0.05$).
Where PLT is Platelet; LYMP is Lymphocyte; and WBC is White blood cells.

0.05). Similarly, when ELVp at 100 and 200 (mg/kg) was co-administered with SA, there was a notable reduction in MDA levels when compared with rats exposed to sodium arsenite ($p < 0.05$).

3.6. Effects of ELVp and sodium arsenite on inflammatory and apoptotic markers in the liver of male Wistar rats

For the expression of inflammatory and apoptotic markers, NF-κB, p53 and BCL-2 were determined. Vitamin E 100 mg/kg, ELVp 100 and

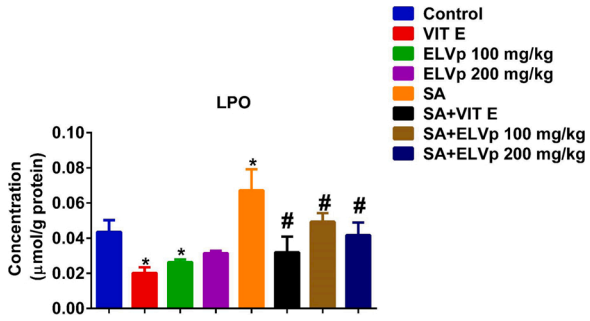


Fig. 6. Effects of ELVp on liver lipid peroxidation of rats treated with sodium arsenite. Concentration of MDA (A). Data are presented as Mean ± SD of 5 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p< 0.05$).

200 (mg/kg) administered to the rats respectively reduced the expression of NF-κB when compared with the control (Fig. 7A, $p < 0.05$). Furthermore, vitamin E 100 mg/kg and ELVp at both treatment doses significantly enhanced the expression of p53 when compared with the control ($p < 0.05$). Although, no tangible difference in SA group when compared with control. However, groups co-administered with SA and Vitamin E or ELVp at both concentrations enhanced the expression of p53 when compared to SA group (Fig. 7B). Consequently, BCL-2 an antiapoptotic protein was significantly increase in SA when put in comparison with control. However, Vitamin E (100 mg/kg) and ELVp 100 (mg/kg) significantly decreased the expression of this protein in comparison with control. Similarly, both co-administration of ELVp and SA decreased the expression of BCL-2 protein when compared to SA only (Fig. 7C, $p < 0.05$).

3.7. Effects of ELVp and sodium arsenite on inflammatory and apoptotic markers in the kidney of male Wistar rats

We investigated similar effect of tested chemical and extract on NF-κB, p53, and Bcl-2 expression through immunohistochemistry on the kidney. In SA-treated rats, NF-κB expression was notably high compared to the control. However, Vitamin E and ELVp groups significantly reduced the expression of NF-κB compared with the control. In addition, co-treatment of Vitamin E and SA significantly reduced NF-κB expression compared to SA-treated rats (Fig. 8A, $P < 0.05$). Furthermore, ELVp (100 and 200 mg/kg) as well as SA and co-administered groups elevated p53 expression in the kidney compared with the control (Fig. 8B). Lastly, the expression of BCL-2 between SA and control was not statically different. However, Vitamin E significantly decreased BCL-2 protein expression compared (Fig. 8C).

4. Discussion

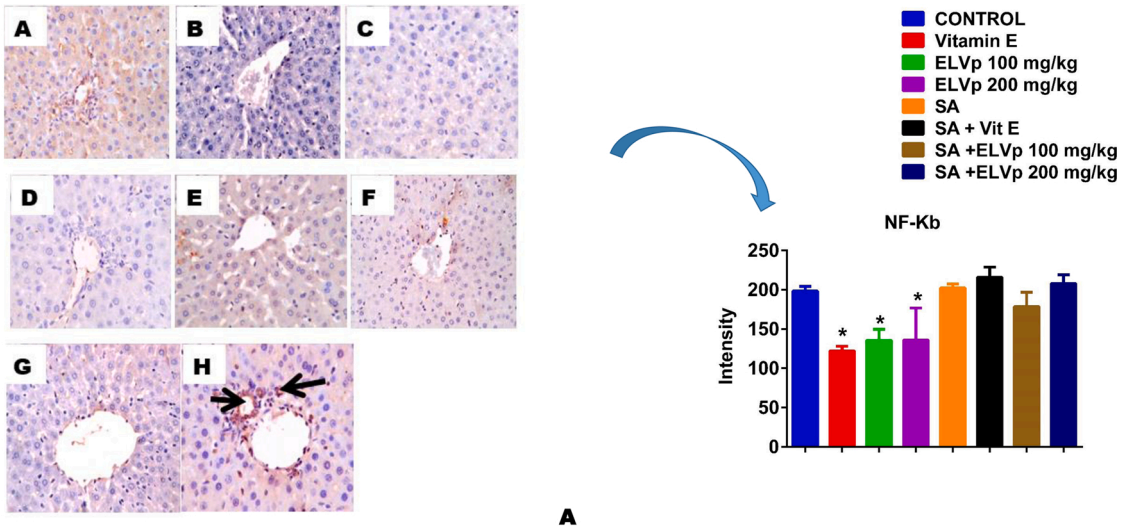
Arsenic is one of the carcinogenic toxicants that humans and animals are frequently exposed to ecologically [35–37]. We investigated the hepato- and nephro-protective effects of *V. paradoxa* leaf extract in sodium arsenite –intoxicated male Wistar rats. In this study, Vitamin E or ELVp significantly increased the change in body weight and relative liver weight. Generally, body and organ weights are nonspecific indicators of well-being in animals. For instance, a decline in body and relative organ weights can be indicating a disease condition [38]. Several authors have reported the effects sodium arsenite on the organ weights of rodents [39–42]. Here, treatment with SA reduced relative kidney weight of rats. This finding corroborates the report of Sakar et al. [43] where SA decreased relative kidney weight of animals. Moreover, ELVp (100 mg/kg) ameliorated SA-induced decrease in relative kidney weight of rats. This observation may suggest the beneficial role of ELVp in the kidney of rats.

The liver is a major organ responsible for regulating several processes in the body system [44]. During liver damage conditions, enzymes like ALT and AST leak into the bloodstream [45]. Our findings revealed that SA increased ALT and ALP activities in rats. This finding corroborates previous reports in which SA increased the activities of these enzymes in the blood of animals [32,46–49]. However, co-administration of SA with ELVp restored AST, ALT and ALP activities comparable with control. This suggest that *Vitellaria paradoxa* possesses hepatoprotective property. Previous study by Fodouop et al. [50], showed that aqueous extract of *Vitellaria paradoxa* leaf was hepatoprotective against *Salmonella typhinum* infection, while Ojo et al. [51] showed *Vitellaria paradoxa* leaf to be hepatoprotective against acetaminophen toxicity. Vitamin E, being a lipophilic antioxidant, reduced ALP activity when compared to SA. This supports the fact that free radical and oxidative stress are the major pointer to liver damage Adetutu et al. [52]. The histopathological analysis of the liver organs affirmed the observation made with the enzyme markers of hepatotoxicity. There was no visible lesion in the liver organs of rats exposed to distilled water, Vitamin E or ELVp 200 mg/kg alone. Rats exposed to ELVp 100 mg/kg alone showed vascular congestion, while those treated with sodium arsenite only showed moderate periportal inflammation, mild increase in connective tissue and vascular nuclei of some cells of the portal triad. Rats co-treated with sodium arsenite and vitamin E or ELVp respectively showed periportal inflammation.

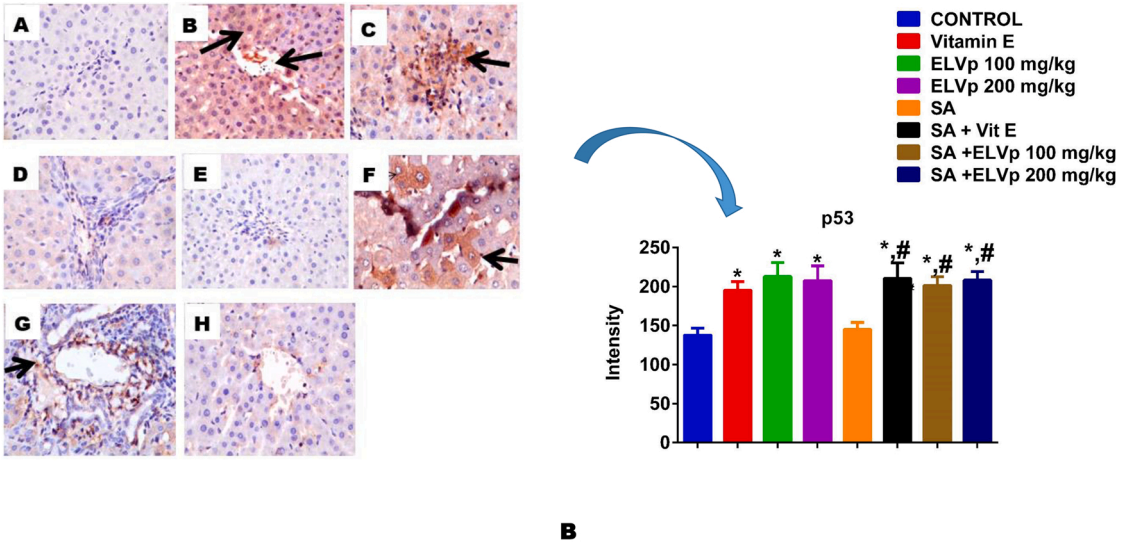
Some studies have implicated SA as a nephrotoxic agent [53–55]. The outcome of ELVp on nephrotoxicity of SA was accessed using the serum urea and creatinine assay. During the splitting of creatine and creatine phosphate in the muscle creatinine is produced [56]. While urea is produced by increased catabolism of protein in mammals. Both creatinine and urea are excreted by the kidney, hence elevated levels of creatinine and urea in the serum is a sign associated with kidney injury [49,57]. The results of serum creatinine and urea showed that SA elevated creatinine and urea concentrations significantly. However, there was reversal when ELVp extract at both concentrations were co-treated with SA. This implies that ELVp was protective against SA-induced nephrotoxicity. This is in line with Turk et al. [13] where SA increased serum urea and creatinine levels. The histopathological analysis of the kidney showed no visible lesion at control, Vitamin E, ELVp 100 mg/kg, ELVp 200 mg/kg and SA + ELVp 200 mg/kg treated rats. In the group treated with sodium arsenite alone there was mild hemorrhagic lesion and peritubular inflammation. However, slight peritubular inflammation was observed for SA + Vit E, while, moderate peritubular inflammation was observed in SA + ELVp 100 mg/kg. This result collaborated the nephron-protective activity of ELVp which was seen in the serum assays.

Moreover, reduction in RBC, HGB and HCT might be triggered by the inhibition of porphyrin or heme synthesis since arsenic is known to cause inhibition of aminolevulinic acid dehydratase activity, thus altering heme synthesis pathway [58]. Our results revealed that SA reduced the RBC, HGB and HCT notably when compared to control. Ola-Davis et al. [10] and Goudarzi et al. [59] revealed same trend of decrease in RBC, HGB, and HCT by SA. However, when co-administered with ELVp, especially at 200 mg/kg, the levels of RBC and HGB improved. This suggest that the plant may have some erythropoietin activity. The exposure of the rats to SA showed significant increases in the platelet, lymphocyte and white blood cell count, which are markers of inflammation which is as a result of antigen antibody reaction against foreign substance in the system.

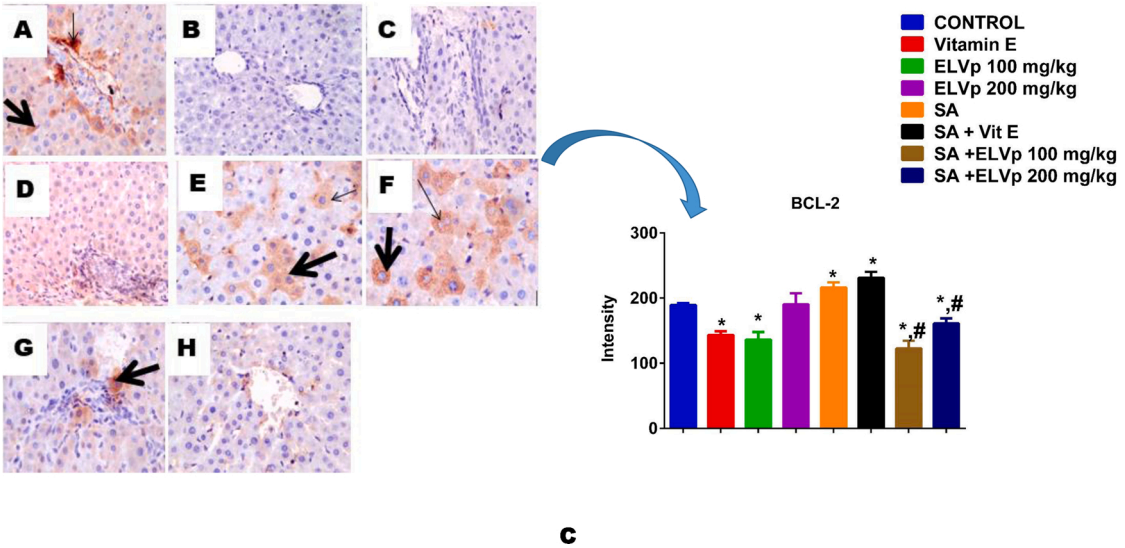
Additionally, enhanced tissue lipid peroxidation is a key feature of oxidative stress induced by arsenic toxicity [38]. Hence, we assayed for lipid peroxidation whose major output is malondialdehyde (MDA) [60]. From our study, the observation that SA increased the level of MDA suggest increase in reactive oxygen species in the treated rats. The reports Morakinyo et al. [61], Odunola et al. [62], Adegoke et al. [11] and Dash et al. [63] indicated induction of lipid peroxidation in the liver, testes, kidney, brain, and uterine of rats exposed to SA. However, our



A



B



C

Fig. 7. Effects of ELVp and sodium arsenite on inflammatory and apoptotic markers in the liver of male Wistar rats. Immunohistochemistry intensity of NF-κB expression (A); p53 expression (B) and BCL-2 expression (C) in liver organ of male Wistar rats. The photomicrographs were labelled as follows: A is control, B is vitamin E 100 mg/kg, C is ELVp 100 mg/kg, D is ELVp 200 mg/kg, E is SA 2.5 mg/Kg, F is SA + Vitamin E, G is SA + ELVp 100 mg/Kg, H is SA + ELVp 200 mg/kg. Data are presented as Mean ± SD of 2 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p < 0.05$).

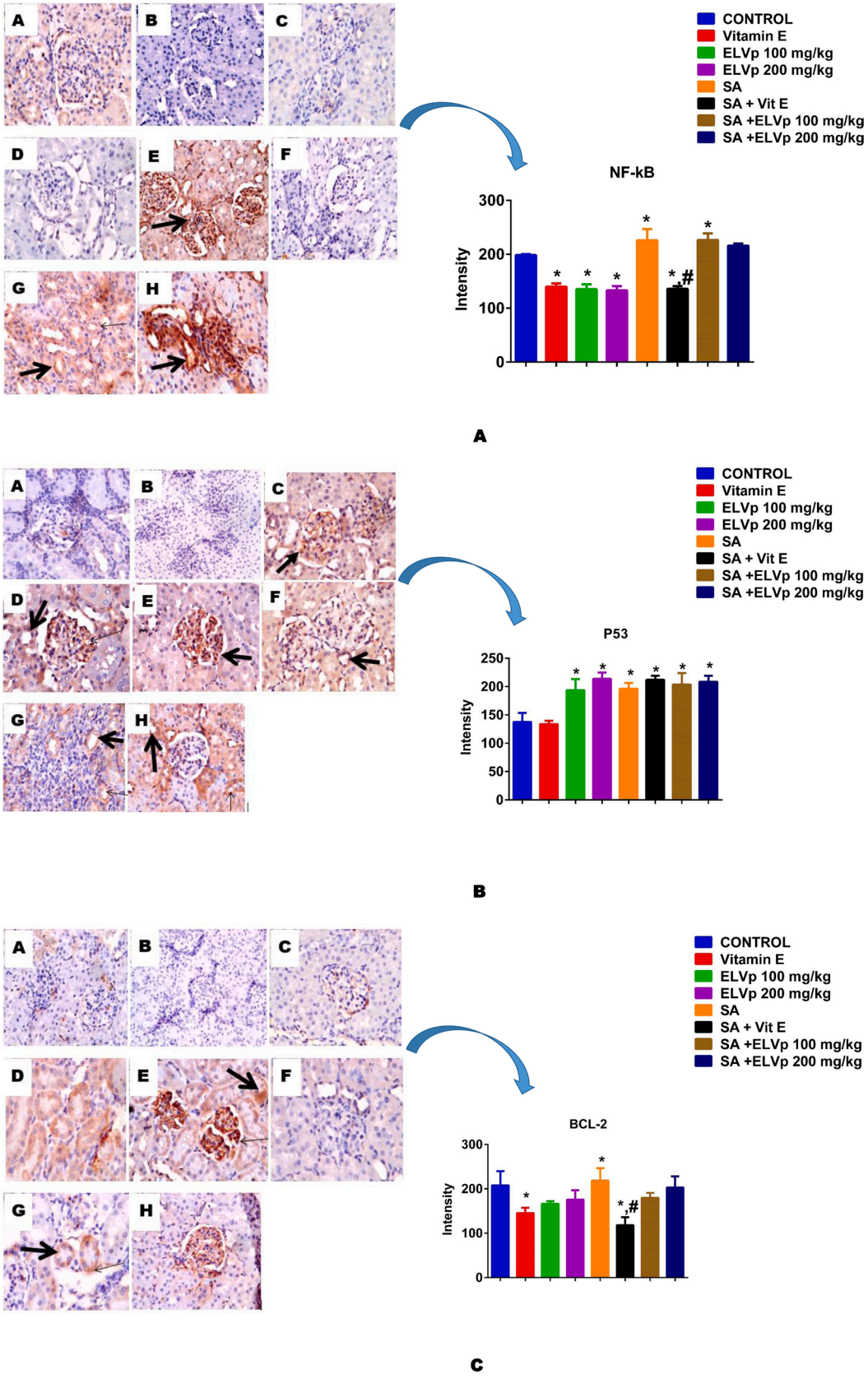


Fig. 8. Effects of ELVp and sodium arsenite on inflammatory and apoptotic markers in the kidney of male Wistar rats. Immunohistochemistry intensity of NF-κB expression (A); p53 expression (B) and BCL-2 expression (C) in kidney organ of male Wistar rats. The photomicrographs were labelled as follows: A is control, B is vitamin E 100 mg/kg, C is ELVp 100 mg/kg, D is ELVp 200 mg/kg, E is SA 2.5 mg/Kg, F is SA + Vitamin E, G is SA + ELVp 100 mg/Kg, H is SA + ELVp 200 mg/kg. Data are presented as Mean ± SD of 2 replicates per treatment group. *Significant difference from the control group at ($p < 0.05$) and # significant difference from sodium arsenite group at ($p < 0.05$).

result indicated that vitamin E and ELVp conferred protection against SA-induced damage. In line with our result, Dash et al. [63] reported that N-acetyl L-cysteine (NAC), used as an antioxidant and anti-carcinogenic agents, reversed the oxidative stress induced by sodium arsenite in the uterine tissue of rats. Recently in our laboratory, Odunola et al. [64] revealed the antioxidant potential of *Vitellaria paradoxa* leaf. Hence, the protection conferred by ELVp and Vitamin E against SA-induced lipid peroxidation confirms their antioxidant property.

Arsenic has been reported to activate pathway associated with NF-κB signaling. Indeed, NF-κB is regarded as the transcription factor that is involved in the crucial process of inflammation [65]. From our result, the inflammatory response to SA exposure may be organ-dependent. The NF-κB expression in the liver had no significant difference when compared to control. However, NF-κB protein was highly expressed in kidney. This differences in organ expression may be attributed to their metabolic processes after absorption. However, in both organs, the Vitamin E and ELVp treatment groups lowered the expression of NF-κB when compared to control. The co-treatment did not reveal any significant difference when compared to SA only.

Furthermore, cellular stress also activates p53 apoptotic pathway which is a trigger for apoptosis and cell cycle control room. p53 induces genes such as BCL-2 and Bax which inhibit and promote apoptosis respectively [66,67]. We noticed SA significantly elevated p53 expression in the kidney. In line with our result, Perveen et al. [68] recently reported that SA up-regulated p53 expression in the uterine of Wistar rats. We further observed that co-administration of SA and ELVp increased the expression of p53 in both organs. This was bolstered by the reduction of BCL-2 expression in the co-treatment group of the kidney. On the contrary, Doxit et al. [69] observed that at the hippocampal sub region of the brain, there was increased expression of BCL-2 when animals were co-treated with alpha lipoic acid and inorganic arsenic. The anti-apoptotic protein BCL-2 is a strategic regulator of apoptosis. Normally, high level of BCL-2 protein expression protect the integrity of the mitochondrial i.e. it prevent the release of cytochrome C [68]. Therefore, we suggest that ingestion of ELVp activate apoptosis via the inhibition of Bcl-2 protein and activation of p53 protein during SA induced inflammation.

5. Conclusion

This study has demonstrated the mitigating effect of *Vitellaria paradoxa* leaf on SA-induced hepatoxicity, nephrotoxicity and disruption of haematological and histological parameters induced by sodium arsenite in Wistar rats. The ameliorative property of the plant might be due to the antioxidant constituents of the plants. However, the anti-inflammatory potential and apoptotic activity is organ-dependent.

CRediT authorship contribution statement

Aghogho Oyibo: Conceptualization, Resources, Carried out Experiment, data analysis, Writing - Original Draft. **Michael A. Gbadegesin**: Data analysis, Writing - review & editing. **Oyeronke A. Odunola**: Supervision, Resources, Data analysis, Writing - review & editing.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors report no declarations of interest.

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