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RESEARCH ARTICLE

Alleviation of Sodium Arsenite Driven Antioxidant Status and Hepatotoxicity by N-Acetyl Cysteine (NAC)

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ABSTRACT

Arsenic has gained popularity for causing multi-organ health ailments. The probable hazardous influence of arsenic stands upon oxidative stress burden and accelerated free radical creation. The usual recovery process against arsenic toxicity has countless opposing consequences. Hence, this experiment was considered to assess the effect of NAC in arsenic imposed antioxidant status and hepatotoxicity. A total of 24 Wistar rats were arbitrarily assigned to four individual groups and the treatment protocol was sustained for 8 successive days. Here, sodium arsenite and NAC was introduced at the dose of 10mg/kg body weight and 100mg/kg body weight respectively. The hepato-renal antioxidant status, serum SGOT, SGPT, urea and creatinine level, status of pro-inflammatory cytokines and hepatic architecture were determined. Sodium arsenite exposed group manifested a remarkably high level of oxidative stress which was further evidenced by diminished antioxidant enzyme levels in hepato-renal tissues. Altered and upgraded level of SGOT and SGPT in arsenic challenged group were a hint of hepatic damage. Along with this, the disarrangement of the cellular structure noticed in hepatic architecture in arsenic exposed group supported hepatoxicity. Moreover, an advanced level of pro-inflammatory cytokines and reduced B-vitamins in the circulation confirmed the toxicity caused by arsenic. NAC application reserved the antioxidant status, improved B-vitamins, and additionally lessened the level of inflammation-causing cytokines and improved the regular histoarchitecture of liver in arsenic ingested animals, suggesting its antioxidant, anti-inflammatory and hepato-protective benefits of NAC.

Keywords: Sodium arsenite, Oxidative stress, NAC, Antioxidant, Hepatotoxicity.

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INTRODUCTION

Arsenic, a deadly metalloid is well recognized for its countless disease occurrences in humans like hepato-renal abnormalities, different classes of cancers, cardiovascular, reproductive, and neurological ailments and so improving the morbidity and mortality proportion [1, 2.]. Among the diverse classes, inorganic arsenic is extremely noxious and people mostly get intoxicated to it from trade pollutants and consumable water [3]. Arsenic and its compounds have the utility for the management of many diseases since ancient time. Even the traditional medicine in China tends to contain high arsenic concentration [4, 5]. After absorption from the gut arsenic has the propensity to sum up mostly in the soft body parts i.e. hepatocyte, cardiovascular tissue, lungs and renal tissue [6]. But the hepatic tissue probably holds the uppermost quantity of arsenic [7]. Epidemiological surveys conducted earlier elucidated that chronic state arsenicosis exhibited liver tumor formation, hepatomegaly, hepatic fibrosis [8] and cytotoxicity [9]. Eventually, hepatocyte is reputed to be the utmost potent site for arsenic carcinogenicity and the probable causative factor for hepatitis proposed by the International Agency for Research on Cancer [10]. Among the plenty of mechanistic events regarding arsenic instigated hepatic toxicity, oxidative stress is evidenced as the principal factual reason [11, 12]. The disproportion of redox stability by arsenic advances reactive oxygen species (ROS) formulation which perhaps intended for oxidation in hepatocyte. This incident further dominated by extreme formation of

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malondialdehyde (MDA) and conjugated dienes (CD) and so lessens the function of superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx) [13, 14]. Many previous reports disclosed that not only oxidative stress but also different cytokines production and many apoptotic proteins upgrades the susceptibility of hepatic toxicity [15, 16]. Peripheral inflammation is propagated by over ROS formation which assist as an inducer of inflammation and modifies the degree of proinflammatory cytokines like IL-6, IL-1β and TNF-α [17]. Besides, higher degree of ROS aided redox signalling is commonly perceived with cellular damage of different macromolecules like DNA, lipids, and proteins which is further negotiated with tissue dysfunction [18]. This cellular damage likely to confined with apoptosis or necrosis gradually. There is over-expression of caspase-3, disparity between Bcl-2 and Bax expression and different structural changes in cell noted in apoptosis [7, 19].

Along with liver, kidney is also a prime target organ of arsenic poisoning as it performs for arsenic excretion [20]. Toxicological reports have proposed that arsenic toxicity could result nephrotic oedema, nephritis, and inflammation related infiltration [21]. Though detailed mechanism on arsenic primed nephrotoxicity in in vivo state has not been well defined.

Therefore, after thorough scrutiny from the past available sources on arsenic linked liver damage, oxidative stress and ROS are the utmost offenders in most cases. Hence, management strategy needs antioxidant administration against arsenic engaged hepatic ,toxicity. N-acetyl cysteine, a good source for glutathione synthesis and also an acetyl derived component of cysteine amino acid [22]. Clinically, NAC has been extensively implemented as antioxidant and a nonprescription remedy without having any confirmed toxicity [23, 24]. Many former reports have introduced that NAC could lessen arsenic caused cytotoxicity, and regulated oxidative stress and ROS formation in many cells like nerve cells [25], liver cells [26], and epithelial cells found in intestine [27]. The thiol group in NAC could maintain the redox homeostasis [28]. It is thought that NAC play a dual role as it is a decent thiol contributor and a nucleophile, thereby NAC may rectify oxidative stress triggered by many toxicants [29]. Alongside, NAC corrected glutathione concentration inside the cell and lessened sequential cell death in numerous internal vital organs and also delayed membrane depolarization in mitochondria [30]. It has immunomodulatory and anti-inflammatory outcomes as well which further endorses for hepatic restoration [31]. NAC has been offered against toxication of numerous carcinogenic metals as chemo-protective drug [32, 33] and has antifibrotic activity too [34]. The exit of different hepatic enzymes like SGOT and SGPT were successfully prevented by NAC via membrane stabilization [28, 35]. Hence, these excellent features of NAC especially defeating oxidative stress might make it a convenient molecule against arsenic treated hepatic toxicity. Therefore, we inspected the outcome of NAC against arsenic driven hepatic toxicity in animal models.

MATERIALS AND METHODS

Materials

Chemicals with analytical grade were used here and supplied by HIMEDIA, MERCK, SRL, Tulip group, India and Ray Biotech, Georgia (USA). NAC was obtained from Sigma-Aldrich, catalog number A7250, purity ≥99% and SDFCL, India supplied sodium arsenite with molecular weight 129.91. IL-6, MT-1 and TNF-α ELISA kits were obtained from Wuhan Fine Biological Technology Co., Ltd. (Wuhan, China).

Experimental animal

Twenty four healthy virgin female albino rats weighing 90-110 g were placed in the animal house of Vidyasagar University, Midnapore, India. They were kept in polycarbonate cages and maintained in a standard laboratory setting. The animals were considered to acclimatized the environment at least 10 days before the commencement of the experiment with indoor temperature 30±2^{0}C and a 12 h dark and 12 h light cycle condition. The animals were allowed to feed on food pellets and water *ad libitum.* The experimental procedures on animals were approved by the ethical committee of the concerned institute as per CPCSEA, Ministry of Environment, Forest and Climate, Government of India.

Experimental Design

Rats were equally and randomly distributed into four separate groups having six rats in each. The treatment protocol was conducted for the 8 successive days. Sodium arsenite and NAC were dissolved in distilled water. The four groups are as follows:

- Group 1: Vehicle treated control.
- Group 2: Rats were treated with sodium arsenite (10 mg/kg body weight) orally for 8 consecutive days through oral gavage.

- Group 3: Rats were treated with NAC (100 mg/kg body weight) orally for 8 consecutive days.
- Group 4: Rats were treated with sodium arsenite (10 mg/kg body weight) plus NAC (100 mg/kg body weight) orally for 8 consecutive days.

At the end of day 8, animals of different groups were anesthetized and euthanized and sacrifice was done and then blood samples and organ (liver) were obtained and preserved in -20°C (minus 20 degree centigrade) in separate germ-free bags. During the whole experimental protocol, the changing pattern of body weights and water drinking capacity was monitored and kept recorded. The hepato-renal indices were measured as per the percentage of total body weight. Here the dose of NAC was selected on the basis of earlier study conducted by Dash et al., 2018 [36].

Estimation of Malondialdehyde (MDA) and Conjugated Dienes (CD) of liver

The liver tissue was homogenised (20% w/v) with homogenising buffer and centrifuged to get the supernatant. Then the supernatant was mixed with thiobarbituric acid and the total mixture was heated in a boiling water bath for 15 min. Afterthat, the mixture was cooled and centrifuged and the supernatant was used to measure MDA at 530 nm (ε=1.56×105 mol^{-1} cm^{-1}) with slight modification [37].

Chloroform–methanol mixture in a ratio of 2:1 was used for the estimation of CD, where liver supernatant was mixed in this solution to extract lipid followed by centrifugation. Finally, lipid was mixed with cyclohexane and reading was taken at 233 nm [38].

Assessment of hepatic and renal antioxidant enzymes by spectrophotometer

The hepato-renal SOD (superoxide dismutase) activity was examined by the formation of blue coloured formazan dye produced by the reaction between superoxide radicals and nitroblue tetrazolium (NBT). Here, xanthine-xanthine oxidase is employed to create superoxide radical. The SOD present in the liver and kidney homogenate suppresses the formazan formation by eliminating the superoxide radicals. The optical density was measured at 560 nm [39,40].

Spectrophotometric evaluation of catalase was executed by the method of Hadwan., 2016 [41]. At first per-chromic acid was formed from dichromate acetic acid which was then converted into chromic acetate by the presence of H_2O_2 after heating. Lastly, this formulated chromic acetate was employed for measuring catalase activity at 570 nm.

Glutathione peroxidase (GPx) activity was quantified using GSH as substrate and calculated as 1 unit equals one micromole of NADPH oxidised in one minute and optical density was obtained at 340 nm [42].

Assessment of hepatic and renal antioxidant enzymes by native gel

At first, liver and kidney tissue homogenate were prepared using 0.1M phosphate buffer and then 50 µg of tissue protein was taken for examining SOD activity on 12% native gel. After the electrophoretic run, a mixture solution was arranged (2.3 milimole nitrobluetetrazolium, 28 milimole TEMED and 28 micromole riboflavin) for staining of the gel in a dark room. After 20 minutes of incubation, colourless bands appeared in a deep blue background [40].

Like SOD, 50 µg of tissue protein was taken for assessing catalase on 8% native gel. After that, 0.003% of H_2O_2 solution was poured into a container in the dark for incubation of the gel after electrophoresis. Then the gel was stained with a staining solution (2% ferric chloride + 2% potassium ferricyanide) until colourless bands appeared in a blue-green milieu [40].

The GPx of liver and kidney tissues were examined in 8% native gel alike with catalase. Here, GSH was treated as a substrate for the proper functioning of GPx. Following the electrophoretic run, the gel was stained with 0.008% of cumene hydroperoxide solution for some time and then the colourless bands appeared after incubation of the gel in a mixture solution of 1% ferric chloride and 1% potassium ferricyanide [40]. Here Image J software has been used for calculating the relative density of bands.

Metabolic toxicity assessment (SGPT, SGOT, creatinine and urea)

For serum glutamic pyruvate transaminase (SGPT) and serum glutamic oxaloacetate transaminase (SGOT) assessment, a common substrate α-ketoglutarate was used. Another substrate called L-alanine and L-aspartate was used for SGPT and SGOT respectively. At 340 nm the optical density was examined [43].

For assessing serum creatinine level, an alkaline medium was created where picric acid reacted with creatinine and formed an orange colour. This colour intensity was taken at 520 nm.

The serum urea level was assessed in the presence

Table 1: Demonstrated the body weight of the animals in various groups throughout the entire duration of the experiment and the metabolic organ's weight. Data were given in mean±SE, n=6. Statistical analysis was accomplished using ANOVA followed by Dunnett t test

	Initial body weight in gm (Mean±SE)	Final body weight in gm (Mean±SE)	Hepato-somatic index in gm%	Renal-somatic index in gm%
Control	109.83±5.71	125.5±6.23	3.07±0.23	0.647±0.033
Sodium arsenite	111.66±4.92	116.16±6.17	3.12±0.1	0.631±0.042
NAC	110.5±4.76	117.5±5.69	3.96±0.3	0.74±0.06
NAC + Sodium arsenite	110.16±5.39	118.33±4.43	3.53±0.16	0.66±0.032

of oxoglutarate and NADH, where ammonia reacted with glutamate dehydrogenase and created glutamate. The optical density was obtained at 340 nm.

Estimation of serum vitamin B_{12} and folic acid, tumor necrosis factor-α (TNF-α), nuclear factor kappa-B (NF-κB), interleukin-6 (IL-6), and metallothionein-I (MT-I) in liver

The c-ELISA was adopted here for evaluating serum level of B vitamins. The procedure was followed as per the manufacturer's instructions in the manual (Wuhan fine test kit, China).

The s-ELISA was implicated for quantification of hepatic TNF-α, NF-κB, IL-6 and MT-I and the procedure adopted here as per the manufacturer's instruction mentioned in the manual (TNF-α- Ray biotech, Georgia, USA; NF-κB, IL-6 and MT-I- Wuhan fine test kit, China).

Histopathology of liver

Liver tissues were immersed in liquid paraffin and block was prepared for tissue sectioning at 5 μm. Then haematoxylin-eosin (Harris) solution was applied here for staining of the tissue sections and the slides were viewed under microscope (Olympus, CX21i, magnification 400×).

Statistical analysis

The hepatic and renal somatic index was denoted as percentage (%) and assessed as weight of the organ which was divided by the weight of the animal and then multiplied by 100 to obtain the result.

All the results were expressed as mean±SE. The sample size (n) in each experimental group was six (6). The significant differences were assessed here between vehicle treated control group and the sodium-arsenite-treated group as well as between the sodium-arsenite-treated group and the supplemented group. One-way ANOVA was implemented here for significance determination, followed by post-hoc Dunnett's test. $p<0.05$ was regarded as the lowest significance level.

RESULTS

Body weight and hepato-renal indices

Table 1 illustrated no differences in body weight in the four different groups between the initial and final body weight in a significant way. The hepato-renal index also provided the same results as no significant diversity was observed between the control group and the sodium arsenite treated group.

Effect of NAC on oxidative stress

The oxidative stress intensity in hepatic tissue has been measured by the assessment of lipid peroxidation end products. As the liver serves as a chief organ for entry and reservoir of arsenic so, hepatic MDA and CD level was significantly hiked in sodium arsenite treated group (*$p<0.05$, **$p<0.01$; Fig. 1A and 1B) rather than the control. NAC, as a super powered antioxidant defended the oxidative stress and its consequences and mitigated sodium arsenite aggravated MDA and CD status in liver in a significant way (#$p<0.05$, ###$p<0.001$; Fig. 1A and 1B).

The spectrophotometric determination of hepatic SOD, catalase and GPx expressed a significant reduction in their level compared with control (***$p<0.001$; Fig.

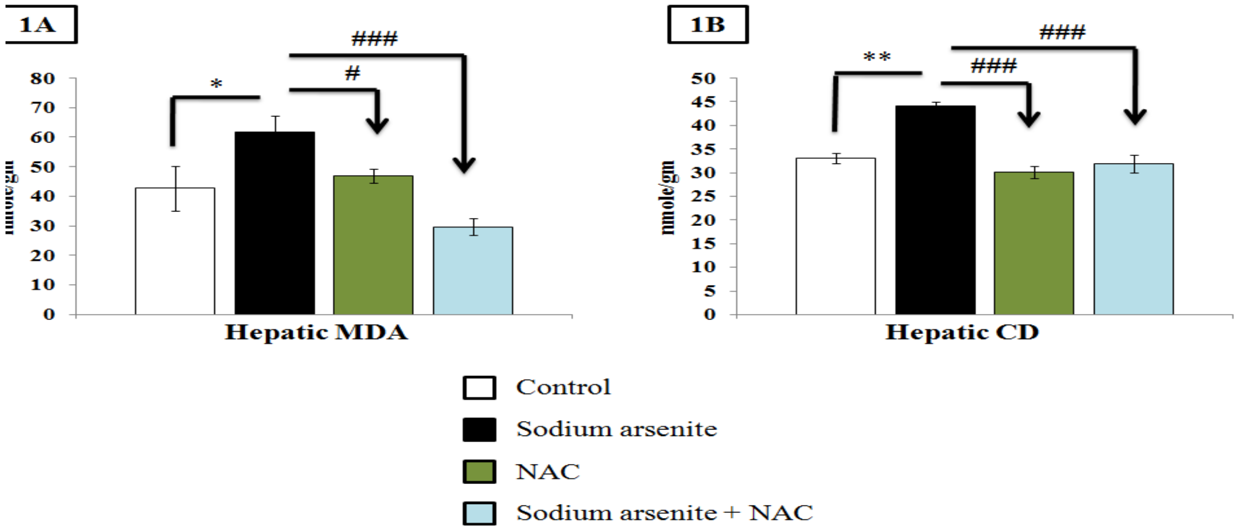
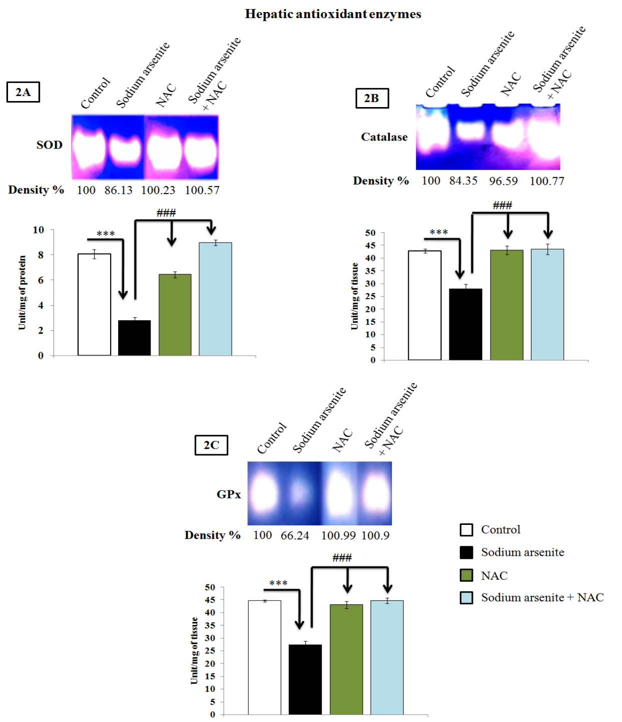


Figure 1A and 1B: Demonstrated the protective consequence of NAC on sodium arsenite persuaded lipid peroxidation outcome in hepatic tissue. Data were given in mean±SE, n=6. Statistical analysis was accomplished using ANOVA followed by Dunnett t test, where *p<0.05 and **p<0.01 were used when comparison is considered between the control and sodium arsenite treated group whereas, #p<0.05 and ###p<0.001 were used when comparison is considered between sodium arsenite treated and other group



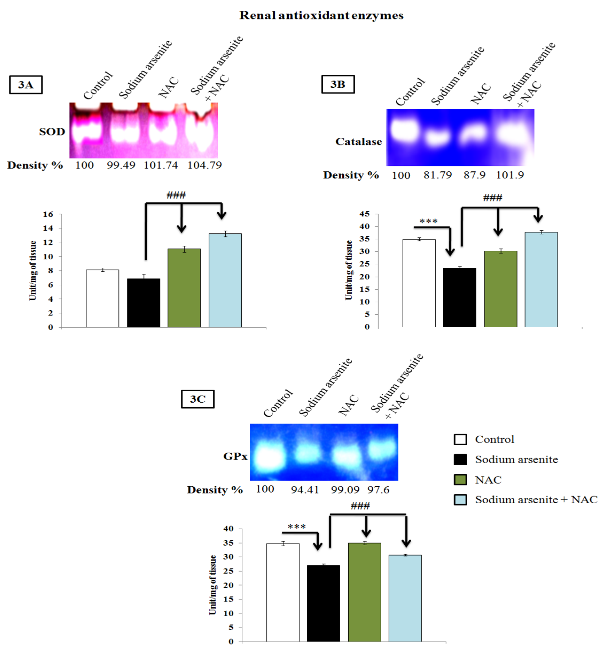


Figure 2A, 2B and 2C: Demonstrated the protective consequence of NAC on sodium arsenite persuaded hepatic antioxidant enzymes like SOD, catalase and GPx. Data were given in mean±SE, n=6. Statistical analysis was accomplished using ANOVA followed by Dunnett t test, where ***p<0.001 was used when comparison is considered between control and sodium arsenite treated group whereas, ###p<0.001 was used when comparison is considered between sodium arsenite treated and other group

Figure 3A, 3B and 3C: Demonstrated the protective consequence of NAC on sodium arsenite persuaded renal antioxidant enzymes like SOD, catalase and GPx. Data were given in mean±SE, n=6. Statistical analysis was accomplished using ANOVA followed by Dunnett t test, where ***p<0.001 was used when comparison is considered between control and sodium arsenite treated group whereas, ###p<0.001 was used when comparison is considered between sodium arsenite treated and other group

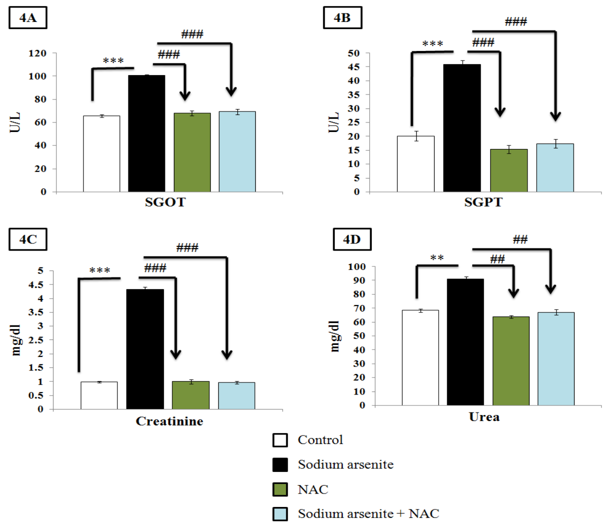


Figure 4A, 4B, 3C and 4D: Demonstrated the protective consequence of NAC on hepatic enzymes and kidney function markers. Data were given in mean±SE, n=6. Statistical analysis was accomplished using ANOVA followed by Dunnett t test, where **p<0.01 and ***p<0.001 were used when comparison is considered between control and sodium arsenite treated group, whereas, ##p<0.01 and ###p<0.001 were used when comparison is considered between sodium arsenite treated and other groups

2A, 2B and 2C). The assessment of these enzymes on native gel also revealed the same outcome as sodium arsenite is the leader for their downward expression. NAC treatment significantly pulled up the activity and expression of these defensive antioxidant enzymes to oppose hepatic oxidative stress (###p<0.001; Fig. 2A, 2B and 2C).

Beside hepatocyte, the measurement of these enzymes was also executed in the renal system. The SOD level was slightly turned down in sodium arsenite consumed group (Fig. 3A). The outcome on native gel reflected the same view as it was mildly depressed by sodium arsenite compared to control (Fig. 3A). Other two enzymes like catalase and GPx were drastically depressed by sodium arsenite (***p<0.001; Fig. 3B and 3C) and native gel band impression also offered the similar answer. Consumption of NAC undoubtedly upgraded the level and expression of all three enzymes significantly (###p<0.001; Fig. 3A, 3B and 3C).

Status of SGOT, SGPT, creatinine and urea (liver and kidney profile)

A drastic and significant upgradation of liver function test markers like SGOT and SGPT level were detected in

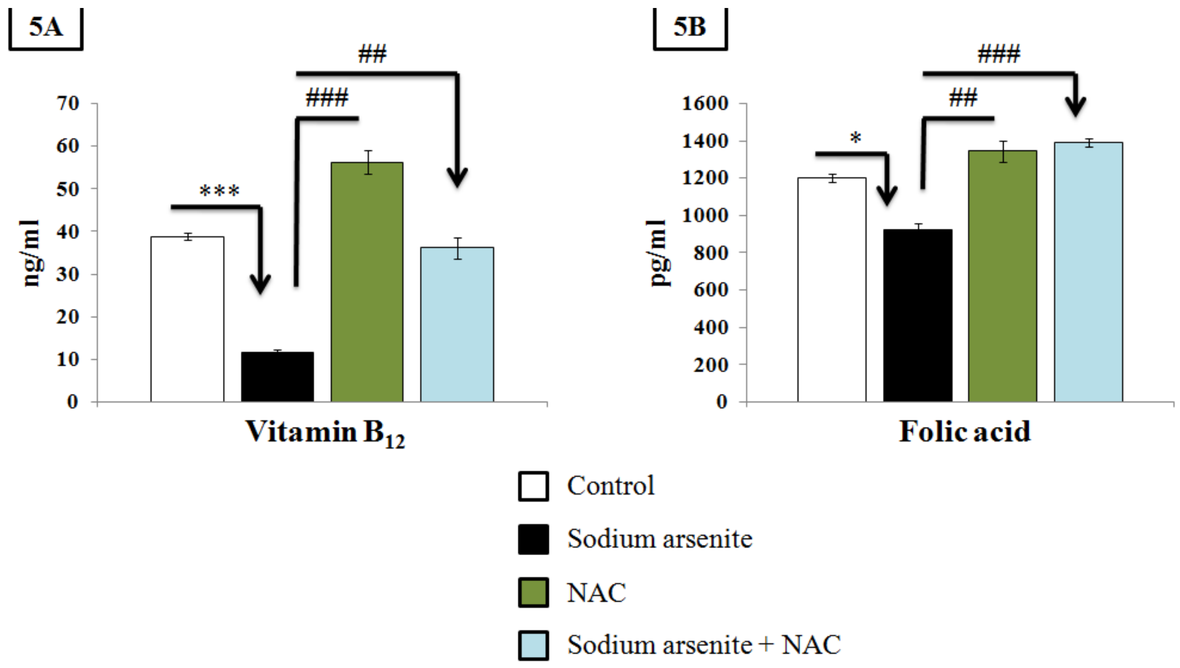


Figure 5A and 5B: Expressed the protective display of NAC against sodium arsenite influenced serum vitamin B_{12} and folic acid. Data were given in mean±SE, n=6. Statistical analysis was accomplished using ANOVA followed by Dunnett t test, where *p<0.05 and ***p<0.001 were used when comparison is considered between control and sodium arsenite treated group, whereas, ##p<0.01 and ###p<0.001 were used when comparison is considered between sodium arsenite treated and other groups

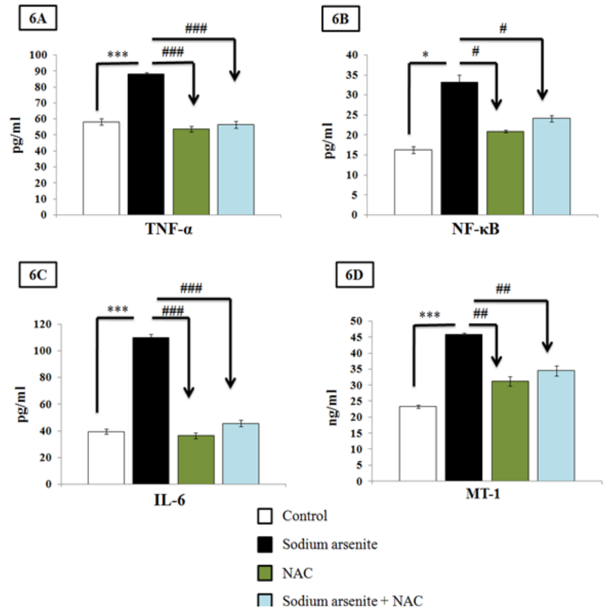


Figure 6A, 6B, 6C and 6D: The role of NAC on inflammatory markers and MT-1 level against sodium arsenite intervening group. Data were given in mean±SE, n=6. Statistical analysis was accomplished using ANOVA followed by Dunnett t test, where *p<0.05 and ***p<0.001 were used when comparison is considered between control and sodium arsenite treated group, whereas, #p<0.05, ##p<0.01 and ###p<0.001 were used when comparison is considered between sodium arsenite treated and other groups

sodium arsenite consumed group (***p<0.001; Fig. 4A and 4B). Likewise, the creatinine and urea levels were also extremely boosted by sodium arsenite treatment (***p<0.001, **p<0.01; Fig. 4C and 4D). This result pointed out that sodium arsenite directed the liver and kidney function towards the abnormalcy. However, co-administration of NAC extensively resettled the concentration of SGOT, SGPT, creatinine and urea towards their circulatory standard value (###p<0.001 for SGOT, SGPT and creatinine and ##p<0.01 for urea; Fig. 4A, 4B, 4C and 4D).

Status of B vitamins

Sodium arsenite treatment notably diminished the B vitamins level (vitamin B_{12} and folic acid) (***p<0.001 and *p<0.05; Fig. 5A and 5B). They played primary function in bioconversion of arsenic. Declining status of these vitamins probably raised the vulnerability of arsenic build up inside the body. However, NAC co-treatment turned up the concentration of vitamin B_{12} and folic acid remarkably and in a significant way (##p<0.01 and ###p<0.001; Fig. 5A and 5B).

Status of inflammatory markers and MT-1

The level of TNF-α, NF-κB and IL-6 were examined in liver tissue to determine the role of NAC on sodium

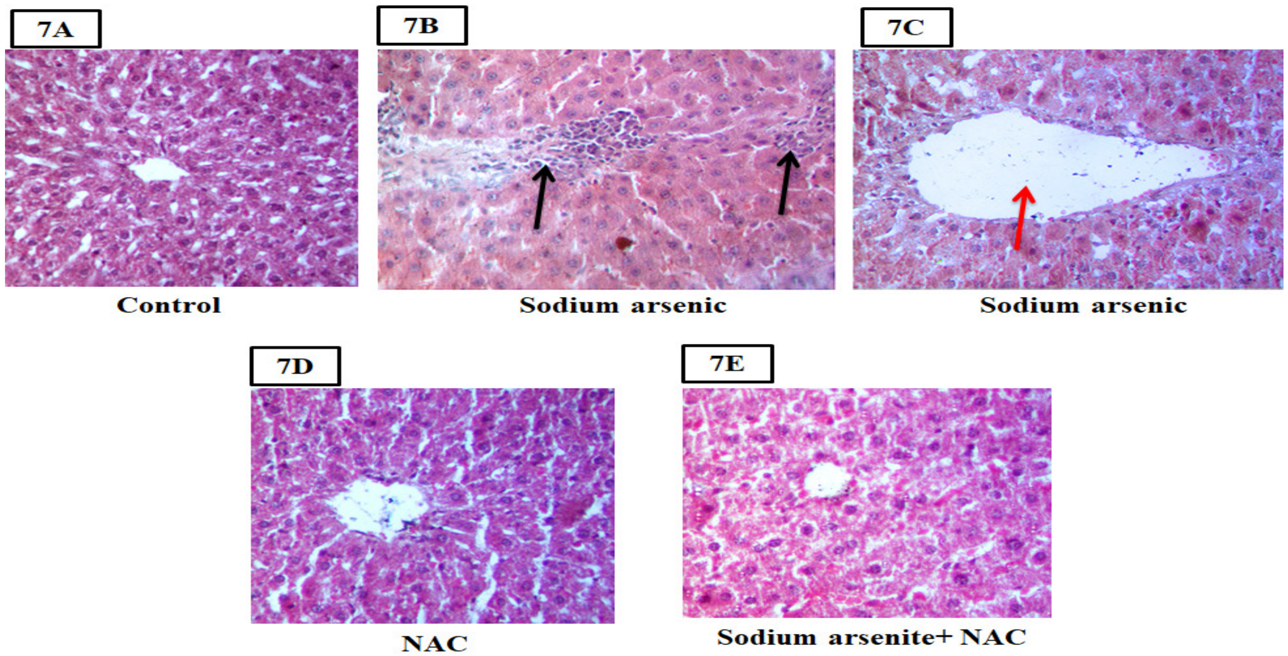


Figure 7: 7A exhibited control group with normal histoarchitecture of liver. 7B and 7C represented the sodium arsenite treated group where severe inflammation (7B black arrow) and increased spaces in the central vein (7C red arrow) were observed. 7D represented the NAC treated group whereas, 7E (sodium arsenite and NAC) manifested improved hepatic architecture with reduced inflammation

arsenite driven inflammation (Fig. 6A; 6B; and 6C). A prompt and significant elevation of these marker's level were seen in sodium arsenite administered group (***$p<0.001$; Fig. 6A and 6C and *$p<0.05$; Fig. 6B). However, concomitant administration of sodium arsenite and NAC downregulated their levels in noteworthy way (###$p<0.001$; Fig. 6A and 6C and #$p<0.05$; Fig. 6B).

Sodium arsenite is responsible for upgrading hepatic MT-1 level as expressed in Fig. 6D (***$p<0.001$). Concurrent treatment of sodium arsenite with NAC depressed its level significantly (##$p<0.01$; Fig. 6D).

Status of liver histology

As displayed in Figure 7, the central vein was surrounded by the regular organisation of hepatocytes. No such hepatic disarrangement, any degeneration, or necrosis was visible in control group (Fig. 7A). In contrast, hepatic inflammation (black arrow), increased space (red arrow) in central vein and overall distortion of hepatocytes were noticeable in sodium arsenite ingested animals (Fig. 7B and 7C). Co-ingestion of NAC repaired the abnormal hepatic histoarchitecture and restored the radial arrangement of hepatocytes with a prominent central vein and minimal hepatic necrosis (Fig. 7D).

DISCUSSION

Various physiological problems including nausea-vomiting, abdominal discomfort, tastes like metal, stupor, and cardiovascular abnormalities characterises acute arsenic exposure, while chronic poisoning executes arsenicosis which is presented by neuropathy, skin depigmentation resembling a 'drop of rain', keratosis and skin cancer [44, 45]. It is indeed a well-known component to induce multiple organ toxicity like nephrotoxicity, immunotoxicity, reproductive toxicity and hepatotoxicity [46]. As the liver itself serves as the prime metabolising area for most xenobiotics, after absorption, arsenic reaches the liver first [47]. Being the storehouse of glutathione, arsenic is detoxified in the liver and becomes ready for biliary excretion. Even the hepatocytes are prospering with arsenic methyltransferase, an enzyme arranged for arsenic methylation and the major location for toxicity [48, 49]. Prolonged half-life and late body excretion during detoxification of arsenic in the liver lead to the expansion of hepatotoxicity as a form of drastic side effect [50].

The prevalence and link between arsenic aggravated toxicity and oxidative stress have been readily established, though the specific mechanistic way is not well defined. Due to the main metabolising site, the hepatocyte is also the primary location for oxidative stress-provoked ROS production [51]. Arsenic-imposed oxidative stress presents simultaneous upregulation of oxidant levels and exhausting antioxidant reserves surpluses the outburst of many pathological circumstances, culminating in lipid peroxidation, damage to proteins, polysaccharides and DNA [52]. Therefore, this experiment evaluated the protective effectiveness of NAC against sodium arsenite applied hepatotoxicity.

The results presented a noticeable upregulation of MDA and CD contents in hepatic tissues following the administration of sodium arsenite (Fig. 1A and 1B). Alongside, the hepato-renal antioxidant stores of SOD, catalase and GPx were also exhausted by arsenic (Fig. 2A, B and C; and 3A, B and C). These events reflect oxidative stress imposed by sodium arsenite and its unfavourable impact on antioxidant enzymes which fundamentally shield the hepatic tissue from oxidative stress. All the aforesaid enzymes are the backbone for handling redox status in the intracellular spaces. The superoxide radicals are generally reduced to hydrogen peroxide by SOD, whereas catalase bears the ability to break hydrogen peroxide into O_2 and water [53]. So, they function together mutually. Additionally, GPx catalyzes lipid hydroperoxide and hydrogen peroxide by using a reducing equivalent called glutathione [54]. Our results exhibited equal trends alike of earlier documentation [53]. Co-management of NAC noticeably yet significantly restored the hepato-renal antioxidant storage. The conformation of thiol group (–SH) and the antioxidant characteristics of NAC may react steadily with ROS [55], and provide safety to the liver against noxious impact of oxidative stress [56].

The status of SGOT and SGPT is vital for assessing liver functionality and to identify hepatic injury if any. This study elicited a definite upsurge in these enzymes in sodium arsenite introduced group (Fig. 4A and 4B). Arsenic could interrupt the natural membrane structure of hepatocytes and possibly increase the cellular penetration capacity and so, leakage of these enzymes in the circulation is elevated [57, 58]. The results obtained here were consistent with the earlier reports [59-61], which denoted arsenic intoxication in hepatic and renal functions. We further measured creatinine and urea levels in serum to check renal function. However, the level of these two important biomarkers was precisely elevated in arsenicated rats (Fig. 4C and 4D). Actually the release of arsenic and its intermediate and final metabolites mostly relies on kidney. Even the kidney assisted in the bioconversion of arsenic, which makes this organ more vulnerable to arsenic exposure and its plausible buildup [62, 63]. Thus, a higher concentration of serum urea-creatinine in rats suggested nephrotoxicity by arsenic (Fig. 4C and 4D).

Folate and vitamin B_{12} synergistically function in the bioconversion of arsenic by helping the abundance synthesis of S-adenosylmethionine (SAM), a methyl contributor in the arsenic conversion process [64, 65]. Here, arsenic exposed rats revealed low serum folate and B_{12} levels (Fig. 5A and 5B), which might be a very supportive motive for accumulation of arsenic in many organs. However, no measurement of arsenic (in quantity/volume) in organs and also in urine was assessed. NAC co-application reflected significantly increased their level. This result is an exact replication of my previous study, where NAC promisingly improved these vitamins' levels [28].

Arsenic, being a major stressor for oxy-stress producer that further causes origination of proinflammatory cytokines like TNF-α, NF-κB and IL-6 and triggers the inflammatory course in the system [66]. Alike this report, the current study expressed an advanced yet significant level of these markers in hepatic tissue (Fig. 6A, 6B and 6C), affirming inflammation that guides to hepatotoxicity and biological membrane abrasions. Sodium arsenite excited proinflammatory NF-κB in hepatocytes through its phosphorylation and cleaved the inhibitor IκB in chorus, switching to prominent TNF-α level [67]. This incident starts the inflammatory chain reaction through maximising IL-6 level which aggravates numerous organ damage [68]. NAC application significantly receded the inflammatory cytokines in hepatic tissue (Fig. 6A, 6B and 6C), signifying that NAC is a powerful anti-inflammatory element. This outcome is in accordance with previous results where NAC pre-treatment receded their level significantly in monocrotophos-induced oxidative stress [68].

MTs perform a crucial function in the regulation and protection of heavy metal equilibrium within the cellular compartment. But exposure to arsenic and associated oxy-stress caused by radicals possessing unpaired electrons and extreme generation of cytokines are accountable for inflammation that causes over-expression of MTs [69-71]. A similar trend was experienced here by the significant upgradation of hepatic MT-I level in sodium arsenite treated group (Fig. 6D). MT counteracts toxicity of numerous heavy metals within its normal range [72], while high level causes cellular damage. Since NAC is a potential oxy-stress reducer therefore, concomitant supply of NAC in arsenite treated rats bestows protection by minimising MT-I level (Fig. 6D).

Henceforth, oxidative stress is the epitome of all constraints by arsenic. Failure of antioxidant activities, upregulation of hepatic enzymes and renal markers in the circulation and induction of pro-inflammatory cytokines have the privilege to confer hepatic injury. Therefore, arsenic group displayed increased hepatocellular lesions, hepatic permeability and infiltration along with inflammation (Fig. 7B), while the control animals exhibited no justified lesions and hepatocytes are organised fruitfully around the central vein (Fig. 7A). This is consistent with earlier data where authors showed dose-dependent toxicity in liver architecture [73]. These hepatic ailments were reverted and a remarkable withdrawal of inflammation was demonstrated when NAC co-application was made in arsenite group (Fig. 7D). Normal hepatic architecture with usual hepatic sinusoids arranged finely around central vein was noticed in arsenite+NAC co-applied group. This outcome agreed with the previous report [74].

Thus, the protective efficiency of NAC in alleviating oxy-stress by arsenic and its accommodated all forms of discrepancies relies on several aspects. NAC is a good source of cysteine, an important component required for GSH synthesis. NAC has the potency of steady deacetylation when it enters the cell and donates the complete cysteine residue for de novo formation of GSH [68]. Hence, NAC improved the cell's antioxidant reserve and quenched the destructive motive of free radicals. Besides, the presence of hydroxyl and sulfhydryl group (thiol group) makes this molecule a suitable agent to chelate toxic heavy metal [75]. Even the thiol group of NAC steadily react with free radicals and hence NAC become a strong antioxidant against ROS [76].

CONCLUSION

The results explained that sodium arsenite exerted hepatotoxicity via oxidative stress. Lower levels of hepato-renal non-enzymatic antioxidants with a consistent upsurge of MDA and CD levels undoubtedly indicated hepatic oxy-stress generation. Moreover, a sharp decline in the status of important B-vitamins, outflow of hepatic enzymes in the circulation and a noticeable structural disturbance of hepatocytes predisposed to hepatotoxicity. Co-application of NAC to arsenite group improved antioxidant status, reduced inflammation and exhibited hepato-protective action by preserving normal sinusoidal structure and limiting infiltration. These outcomes significantly pointed out that NAC could be a prevailing therapeutic agent against sodium arsenite-assisted hepatic toxicity. However, additional study is required to understand the mechanistic way of removing arsenic and its deliberate noxious consequences by NAC.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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