

Armejavine Ameliorates Acetaminophen-Induced Acute Liver Injury by Inhibiting Oxidative Stress and Inflammation

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ABSTRACT

Objectives: The liver is an essential organ that plays a vital role in detoxification and protection against harmful chemicals and toxicants. Nursing care for patients with liver disorders needs a comprehensive understanding of the disease, probable outcomes, and suitable nursing interventions. The present work was focused on assessing the hepatoprotective properties of Armejavine (ARM) against Acetaminophen (APAP)-induced liver damages in rats. **Materials and Methods:** A total to thirty male Wistar rats were distributed into 5 groups ($n=6$ /each group). Group I was standard control, whereas Group II was administered with APAP (250 mg/kg) to cause hepatotoxicity. Groups III and IV underwent pretreatment with two doses of ARM (10 and 20 mg/kg, respectively) before to APAP exposure, whilst Group V was administered with silymarin (100 mg/kg) as a standard drug. Liver marker enzymes, serum biochemical parameter levels, oxidative stress indicators, antioxidant levels, and inflammatory markers (tumor necrosis Factor- α [TNF- α], Interleukin [IL]-6, and IL-1 β) were assessed using kits. The histopathological analysis was performed in the liver tissues. **Results:** the pretreatment with ARM markedly diminished the concentrations of liver dysfunction markers aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), total bilirubin, Nitric Oxide (NO), Malondialdehyde (MDA), and inflammatory cytokines (TNF- α , IL-6, and IL-1 β) in comparison to the APAP group. The hepatoprotective effects of ARM were found to be similar with those shown in the silymarin-treated group. ARM treatment also diminished liver weight and significantly improved antioxidant defenses, including the Superoxide Dismutase (SOD), Glutathione (GSH), and Catalase (CAT) levels. The findings of histopathological studies of liver tissues were further evidenced the hepatoprotective properties in ARM. **Conclusion:** The present work suggested that ARM has considerable hepatoprotective activities against APAP-induced liver damages by enhancing antioxidant mechanisms and alleviating inflammatory responses. These results reinforce the therapeutic efficacy of ARM and suggest its conventional therapeutic application for liver protection.

Keywords: Acetaminophen, Antioxidant, Armejavine, Hepatic Markers, Liver Injury.

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INTRODUCTION

The liver is the largest internal organ in the body and performs a several crucial functions. It is particularly vulnerable to a several damages and diseases due to its diverse functions and advantageous location. Unfortunately, liver diseases are often neglected in underdeveloped nations, where they have a significant negative impact on public health and highlight the urgent need for knowledge and action.¹ The impact of liver disease on morbidity and death is particularly noticeable in

lower-income countries, making the burden of liver disease more than just a number.² Numerous medications, toxins, and herbal medicines have been linked to liver damage; in fact, 20–40% of cases of hepatic failure are caused by drugs.

In Western society, the most common cause of acute liver damage is acetaminophen overdose.³ N-Acetyl-P-Aminophenol (APAP) is the chemical name for paracetamol, also referred to as acetaminophen. This popular drug reduces fever and acts as a reliable antipyretic, which lowers temperature, as well as an analgesic, which relieves pain.⁴ But it's important to use cautious because taking too much acetaminophen can seriously harm the liver.⁵ It becomes a powerful hepatotoxin when consumed in lethal quantities, causing severe damage to the liver and kidneys that can be fatal to humans as well as many other animals, including rats.² More than half of all cases of ALF are caused by APAP-Induced Liver Injury (AILI), making it the leading cause



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of ALF in both the US and Europe. Consequently, proactive monitoring and potential AILI treatment is essential since they can both considerably lower the incidence of ALF and enhance the prognosis for affected individuals, paving the way for enhanced health outcomes.⁶

The successful treatment of hepatic diseases continues to be a major challenge for current medical science. The only drugs now prescribed for liver diseases are immunosuppressive and corticosteroids drugs. Nonetheless, these drugs are often demonstrate numerous unfavorable side effects.² Therefore, there is an unmet need for novel drug candidates that are both safe and potential, as well as affordably priced. In therapeutic settings, silymarin and N-Acetylcysteine (NAC) are currently the most effective drug candidates for the treatment of AILI, they both often exhibit several side effects. *Nelumbo nucifera*, commonly referred to as the sacred lotus, is an exceptional food and medicinal plant prevalent across Asia. Renowned for its medicinal properties, it has historically been employed to address several conditions, including infections, fever, diarrhea, and hemorrhage. *Nelumbo nucifera* is a significant asset for health and wellness due to its extracts, which are particularly distinguished for their potent antioxidant qualities and exceptional free radical scavenging capabilities.⁷ *Nelumbo Newkifera* is a wonderful medicinal plant that yields the appealing active component known as Armepavine. Recent research has shown that it exerts significant anti-inflammatory effects on human peripheral blood mononuclear cells, namely in lupus nephritic mice and T lymphocytes.⁸

It has already been highlighted the hepatoprotective and antioxidant properties of *Nelumbo nucifera*-derived bioactive compounds. It has been already suggested that *N. nucifera* seedpod extract mitigated the APAP-induced liver damages,⁹ while Li *et al.*, (2023) and Służały *et al.*, (2024) suggested the protective activities of natural products against hepatic oxidative stress and inflammation.^{10,11} Recent study further emphasized the therapeutic promise of *N. nucifera* alkaloids, including armepavine,¹² and Nematallah *et al.*, (2024) provided mechanistic support for phytochemical antifibrotic actions through molecular docking and formulation studies.¹³ The therapeutic potential of Armepavine (ARM) in liver fibrosis remains complex and not yet fully elucidated, as its precise mechanisms of action require further clarification through mechanistic and preclinical studies.

Nursing care is essential for the early identification, treatment, and recovery of patients with APAP-induced hepatotoxicity in clinical and hospital settings. Nurses are critical in monitoring changes in liver enzymes, identifying clinical symptoms such as jaundice or stomach pain, assisting detoxification, and keeping patients hydrated. To reduce liver damage and improve patient recovery outcomes, evidence-based nursing practices emphasize the significance of combining supportive and pharmaceutical therapies. As a result, the discovery of novel hepatoprotective

agents improves clinical and nursing tactics for managing drug-induced liver injury, while also advancing pharmacological treatment. The primary goal of this study is to induce liver injury in the experimental rats using APAP and further assess if armepavine can protect the APAP-induced liver toxicity. We assessed liver functionality using biochemical indicators and other relevant parameters. We also evaluated the antioxidant potential of armepavine in liver tissues. We also examined the histological alterations to identify important therapeutic aspects of armepavine and to understand its function in the management of liver damage.

MATERIALS AND METHODS

Ethical approval

The present work was approved by the Ethics Committee of Shanxi Bethune Hospital (Approval Number: YXLL-2024-266). All experimental procedures involving animals were performed as per the institutional guidelines for the care and use of laboratory animals.

Materials

All chemicals, reagents, assay kits, and equipment used in this study were commercially obtained and made available prior to the initiation of the experiment.

Experimental animals

A total of thirty (30) male Wistar rats were used in this study. The animals were obtained from a certified animal facility with ethical authorization for the supply of laboratory animals. The rats were housed in polycarbonate cages under standard laboratory conditions, maintained on a 12-hr light/dark cycle at an ambient temperature of 21–25 °C, with free access to standard pellet diet and drinking water. After an acclimatization period, the animals were randomly assigned into five groups ($n=6$ per group) based on body weight. A timeline schematic illustrating the dosing schedule and sacrifice of the study were shown in Figure 1.

Group I (Control): received distilled water only.

Group II (APAP): received Acetaminophen (APAP) at a dose of 250 mg/kg orally for five consecutive days. The total duration of the study was 14 days in the current year.

Group III (ARM 10 mg/kg+APAP): received Armepavine (ARM) at 10 mg/kg orally for five consecutive days, followed by APAP (250 mg/kg) for another five days.

Group IV (ARM 20 mg/kg+APAP): received ARM at 20 mg/kg orally for five consecutive days, followed by APAP (250 mg/kg) for another five days.

Group V (Silymarin+APAP): received the positive control Silymarin (SIL) at 100 mg/kg orally for five consecutive days, followed by APAP (250 mg/kg) for another five days.

Sample collection

At the end of the treatment period, the animals were anesthetized and euthanized. Blood samples were collected via cardiac puncture into clean, heparinized tubes and allowed to clot at room temperature. Serum was separated by centrifugation at 2500 rpm for 15 min and used for biochemical analyses. The livers were carefully excised, rinsed in cold 0.9% NaCl solution, and divided into portions for biochemical and histopathological examinations. For biochemical assays, liver tissues were homogenized in ice-cold 0.9% NaCl buffer and stored appropriately until analysis.

Effect of Armepavine against APAP-induced Hepatotoxicity on liver weight.

The animals were given anesthesia following a 24-hr induction of liver toxicity, and blood was drawn to assess additional parameters. Further, following cervical dislocation, the animals were slaughtered, and their liver tissue was taken out, weighed, and kept at -80 °C for additional examination.¹⁴

Effect of Armepavine on the liver enzymes in serum

Biochemical indicators such as AST, ALP, and total bilirubin were evaluated for liver function using spectrophotometric testing with a commercial kit.¹⁵

Effects of Armepavine on Hepatic Oxidative Stress Biomarkers

After weighing and rinsing the liver of each rat, it was homogenized in cold potassium phosphate buffer using ice-cold saline at a concentration of 0.05 M and 7.4 pH. After centrifuging the homogenate at 10,000Xg for 15 min at 4°C, the supernatant was used to test the oxidative stress. To assess lipid peroxidation, Malondialdehyde (MDA) levels were measured.¹⁶

Griess reagent, consisting of a mixture of reagents such as 1% sulfanilamide, 0.1% NED, and 2.5% phosphoric acid, was used to test the tissue amount of nitrite, a marker of NO generation. Griess reagent and hippocampal homogenate sample were combined in equal amounts, and the mixture was allowed to sit at room temperature in a dark environment for 10 min. The absorbance at 520 nm was measured using a microplate reader. Ultimately, the sodium nitrite calibration curve was used to calculate the nitrite level, which was then shown as $\mu\text{mol}/\text{mg}$ protein.¹⁷

Effects of Armepavine on Hepatic Antioxidant Enzyme Activities

Glutathione, catalase, and superoxide dismutase were measured in the liver homogenate. SOD levels were calculated using the Magwere *et al.*, (1997)¹⁸ with slight modification. Estimation of CAT. The liver homogenate was assayed for catalase colorimetrically at 620 nm and expressed as μmol of H_2O_2 consumed/min/mg protein.¹⁹ Estimation of GSH was determined in the liver homogenate using the method of Ellman.²⁰

Effects of Armepavine on hepatic concentrations of inflammatory Biomarkers

Serum levels of the inflammatory factors IL-1 β , TNF- α , and IL-6 were measured using commercial kits. All steps were carried out in compliance with the manufacturer's procedure.²¹

Study of the histopathological impact of Armepavine on the liver

The liver samples, which were about 5 mm thick, were embedded in paraffin after being dried using several grades of ethanol solutions. A rotary microtome was used to cut the tissue into 4-micron-thick pieces after the block was embedded in paraffin was prepared using an automatic tissue processor. For histological analysis, the samples were examined under a microscope after being colored with Hematoxylin and Eosin (HandE).¹⁴

Statistical Analysis

The information was given as mean $\pm$ SD ($n=6$) and was obtained from three different tests. Quantitative variables were analyzed by using the GraphPad Prism program. The Tukey *post hoc* test for multiple comparisons was used to compare group means. $p<0.05$ indicated a statistically significant difference between the groups.

RESULTS

Effects of Armepavine against APAP induced Hepatotoxicity on liver weight.

Figure 2 shows the administration of APAP resulted in a striking increase in liver weight when compared to the normal control group. On the other hand, the weight of liver tissue significantly decreased in the armepavine-treated groups, and this drop increased with increasing armepavine concentrations. The effects, however, were not as noticeable as those in the positive control group, where rats given silymarin showed notable variations in liver weight.

Effects of Armepavine on the liver marker enzymes in the serum of APAP-intoxicated rats

We carefully analyzed serum levels of liver enzymes to assess liver damage. When compared to the control group, wistar rats given only Acetaminophen (APAP) showed a substantial increase in important blood markers such as total bilirubin, ALP, and AST, indicating severe hepatocellular injury. Though, the different concentrations of armepavine-treated rats resulted in a marked reduction in the total bilirubin, AST, and ALP levels. These findings were found similar those noted in the silymarin-treated rats (Figure 3).

Effects of Armepavine on the oxidative stress markers in liver tissues

The levels of oxidative stress markers MDA and NO were assessed in the experimental rats, with findings are depicted in Figure

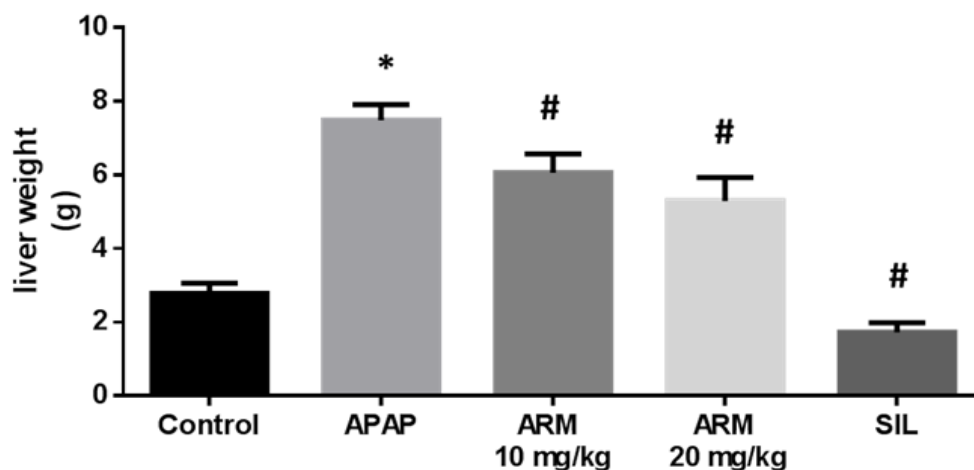


Figure 1: The effect of Armepavine (ARM) against APAP is inspired by hepatotoxicity on the liver weight. Each point represents the average $\pm$ SD on six rat. * Important difference compared to the control group ($p < 0.05$). # Significant difference compared to the Acetaminophen (APAP) group ($p < 0.05$).

4. The current results suggested that the APAP (250 mg/kg)-induced rats had significantly elevated levels of NO and MDA in comparison to control. Interestingly, the armepavine treatment at a dosages of 10 and 20 mg/kg markedly diminished the NO and MDA levels in the APAP-induced rats, demonstrating a considerable protective effects against oxidative stress caused by APAP.

Effects of Armepavine on Hepatic Antioxidant Levels

In this work, the concentrations of antioxidants were evaluated in the control and experimental rats, and the findings are given in Figure 5. As indicated in Figure 5, a considerable diminution in SOD, CAT, and GSH levels were observed in the APAP-induced rats, which indicates the onset of severe oxidative damage. Whereas, the armepavine treatment and standard drug silymarin showed marked increase in the levels of these antioxidants in the APAP-induced rats. Specifically, the treatment with armepavine effectively restored the liver's antioxidants GSH, CAT, and SOD levels in the APAP-induced rats. These findings are found similar to those observed in the standard drug silymarin treatment.

Effects of Armepavine on hepatic concentrations of inflammatory Biomarkers

In this work, we investigated the levels of inflammatory cytokines in the control and treated rats with results illustrated in Figure 6. The current findings indicated the significant augmentation in the TNF- α , IL-1 β , and IL-6 levels in the APAP-induced rats. Whereas, the treatment with armepavine at concentrations of 10 and 20 mg/kg exhibited a considerable ability to diminish the TNF- α , IL-1 β , and IL-6 levels in the APAP-induced rats. This illustrates the potential protective effects of Armepavine against the inflammatory response induced by acetaminophen overdose.

Histopathological alterations in the liver following Armepavine treatment

Figure 6A illustrates an unaltered liver segment from a control rat, displaying the usual histological structure of hepatocytes around the main vein and no histopathological changes. In Figure 6B, the liver tissue from an APAP-treated rat shows severe congestion and dilation of the portal vein, followed by edema and the infiltration of inflammatory cells in the periductal tissue around the bile ducts that have dilated cystically. Figure 6C depicts ARM (10 mg/kg) treated rats, which exhibit congestion in the portal vein along with mild inflammatory cell infiltration near the bile ducts. Figure 6D, shows ARM (20 mg/kg) treated rats that display minimal visible alterations. Finally, Figure 6E presents liver tissue treated with silymarin, which appears to have nearly normal hepatic architecture.

DISCUSSION

Age, dietary status, genetic background, gender, lifestyle factors, obesity, drug exposure, and dosage are some of the variables that affect drug-induced hepatotoxicity.¹⁴ Drug-Induced Liver Injury (DILI), which includes liver damage from chemical drugs, is a common clinical adverse pharmacological reaction. ALF and patient death may result from severe episodes of DILI, which is the main cause of ALI. According to clinical studies, DILI is becoming more prevalent and is currently the third most common reason for liver disease, after fatty liver disease and viral hepatitis. At prescribed dosages, APAP is a safe and effective antipyretic and analgesic, but because of its hepatotoxicity, an overdose may cause ALI.¹⁹ Thus, finding innovative therapeutic approaches is essential for APAP-induced liver failure, especially in the latter stages of injury.³

Determining the impact of dimensions and underlying liver disease sensitivity is a frequent challenge for forensic pathologists.

Studies show that steatosis and hepatic fibrosis do refrain from making liver tissue more susceptible. Numerous other factors may influence the liver tissue's vulnerability in addition to its innate resistance. When assessing the potential impacts of structural alterations on liver size, weight, tissue resistance, and vulnerability are all taken into consideration. As a result, the present study evaluated how ARM affected liver weight due to histological alterations. It was demonstrated that ARM reduced liver weight in rats given APAP and that its effects diminished as concentration increased. Significant effects comparable to those of rats treated with reference standard and normal rats would be demonstrated by increasing the concentration of ARM dose. Biochemical indicators like AST, ALP, and bilirubin levels were assessed to assess liver damage. In our investigation, increased levels of biochemical markers such as AST, ALP, and total serum bilirubin validated the hepatotoxicity caused by acetaminophen. The cells of the liver parenchyma are most commonly associated with AST. Elevated AST levels are indicative of acute liver damage. ALP levels are also raised by infiltrative liver diseases and intrahepatic cholestasis.² Normally, the cytoplasm, microsomes, or mitochondria contain these enzymes. When liver cells' transport function is disrupted due to hepatotoxicity, the plasma membrane leaks, which causes these enzymes to leak and raises their blood level.¹⁵ When treated with hepatotoxin, a high quantity of bilirubin in serum indicates the rate at which liver injury is

causing erythrocytes to degrade. ARM pretreatment greatly decreased the increased levels of AST, ALP, and bilirubin in rats treated with APAP. Reduced levels of these serum indicators may be due to the stimulation of hepatocellular protein synthesis and the capacity to stimulate microsomal enzymes either by speeding up the excretion of paracetamol or by reducing oxidative stress brought on by paracetamol. Treatment with silymarin reversed the elevated levels of ALP, AST, and total bilirubin.

This study assessed oxidant/antioxidant indicators such as LPO in terms of MDA and NO, which are significant contributors to APAP-induced hepatotoxicity in oxidative stress. MDA levels are measured as a proxy for cellular membrane damage and structural alterations. The increase in MDA levels, a hazardous byproduct of lipid peroxidation, provided additional proof in this study that APAP is implicated in the generation of oxidative stress. The failure of antioxidant defense mechanisms is shown by the increased MDA in the liver. It is commonly known that the liver tissue of animals intoxicated with paracetamol without treatment has a higher level of lipid peroxidation than that of other treated groups, compared to high Polyunsaturated Fatty Acid content (PUFA), which is susceptible to peroxidative damage.⁴ These effects were considerably restored by using silymarin or an extract as a pretreatment. Effects of APAP on the NO synthase may be linked to elevated NO. When glutathione

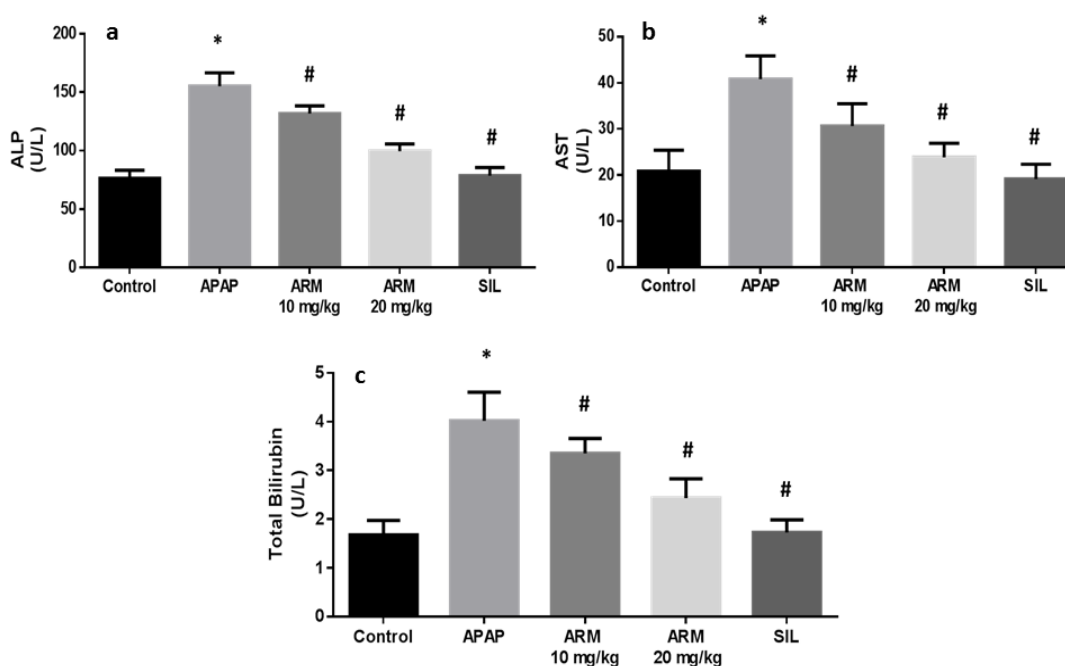


Figure 2: Effect of Armevavine (ARM) on serum liver enzymes (a) ALP, (b) AST, and (c) total bilirubin in acetaminophen-induced liver damage in rats. Each point represents the mean $\pm$ SD of six rats. * Significant difference compared with the control group ($p<0.05$). # Significant difference compared with the Acetaminophen (APAP) group ($p<0.05$).

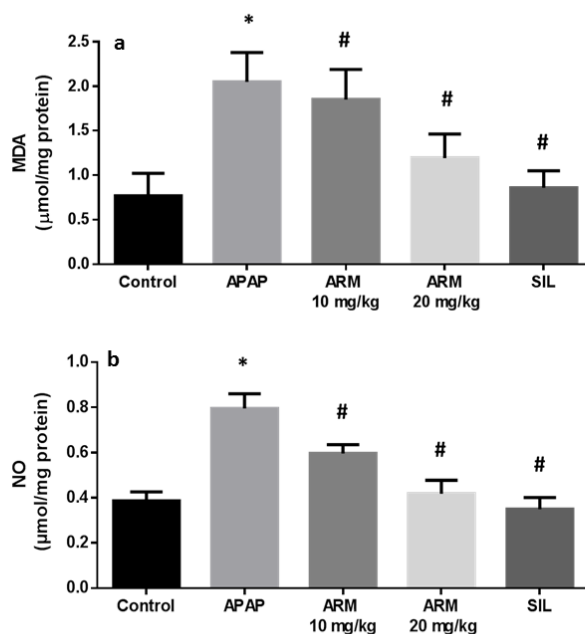


Figure 3: Effects of Armepavine (ARM) (10 and 20 mg/kg) on hepatic oxidative stress biomarkers (a) MDA $\mu\text{mol/mg}$ protein and (b) NO $\mu\text{mol/mg}$ protein respectively, in APAP-exposed Wistar rats. Each point represents the mean $\pm$ SD of six rats. * Significant difference compared with the control group ($p<0.05$). # Significant difference compared with the acetaminophen (APAP) group ($p<0.05$).

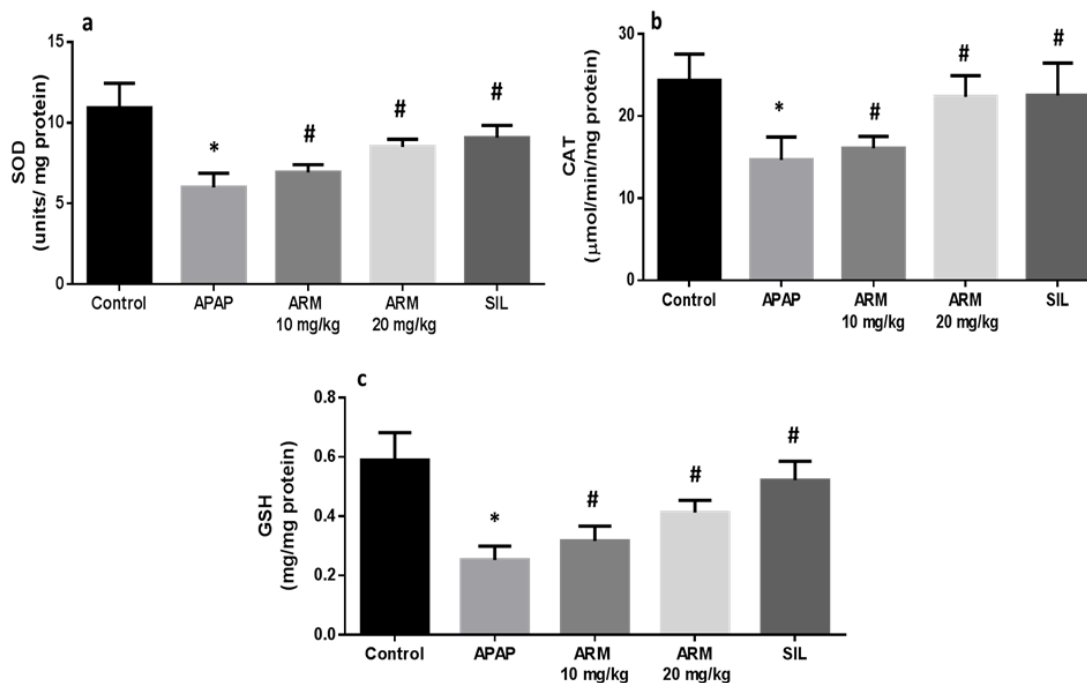


Figure 4: Effects of Armepavine (ARM) (10 and 20 mg/kg) Hepatic Antioxidant Enzyme Activities. (a) SOD (units/ mg protein), (b) CAT ($\mu\text{mol/min/mg}$ protein), and (c) GSH (mg/mg protein) respectively in APAP-exposed Wistar rats. Each point represents the mean $\pm$ SD of six rats. * Significant difference compared with the control group ($p<0.05$). # Significant difference compared with the Acetaminophen (APAP) group ($p<0.05$).

is not present, the excess NO combines with superoxide to form a reactive intermediate known as peroxynitrite, which causes protein nitration. However, hydrogen peroxide and peroxynitrite are thought to be the main contributors to lipid peroxidation. LPO is a type of radical reaction that causes cell death and the breakdown of polyunsaturated fatty acids in lipid membranes. MDA and NO hepatic levels dropped with ARM delivery, which can be connected to the liver tissues' improved thiol molecule quality and antioxidant ability.

The presence of ROS (Reactive Oxygen Species) over the antioxidant buffering level results in oxidative stress. ROS, such as superoxide, hydroxyl radicals, and singlet oxygen, are linked to APAP-induced hepatotoxicity and play a significant role in the pathophysiology and progression of liver diseases. By increasing the amounts of naturally occurring antioxidant enzymes such as GSH, CAT, and SOD, antioxidants seem to counteract disease processes by reducing lipid peroxidation.⁴ Numerous studies have demonstrated that ROS can change the composition and capabilities of cells, tissues, organs, and systems by damaging lipids, proteins, and DNA. Superoxide anions are converted to Hydrogen peroxide (H_2O_2) by the efficient defense enzyme SOD. All aerobic cells include the hemoprotein catalase, which catalyzes the transformation of H_2O_2 and converts it into water and oxygen while shielding the tissue from oxidative damage brought on by highly reactive oxygen and hydroxyl free radicals.

As a non-enzymatic antioxidant, GSH reduces the toxicity of xenobiotics, Hydroperoxides (ROOH), and H_2O_2 , making it an incredibly effective intracellular buffer against oxidative stress. These enzymes that are antioxidants are readily inactivated by lipid peroxides or other ROS, which lowers their activity in APAP toxicity.⁴ In the current investigation, the administration of APAP was substantially associated with decreased liver GSH activity and SOD and CAT levels. Pretreatment with ARM restored GSH levels that were comparable to the positive control by reducing APAP-induced GSH depletion and inhibiting CAT and SOD activity. Immune cell activity is suppressed by acetaminophen liver damage.⁹

According to this study, APAP-induced ALI rat models showed considerably higher amounts of IL-1 β , IL-6, and TNF- α , three pro-inflammatory cytokines, whereas ARM pretreatment greatly decreased these levels. One of the hallmarks of ALI pathology is an inflammatory response, which frequently follows the illness's development.⁸ Our *in vitro* results line with the previous data, where studies imply that Arm suppressed TNF- α -stimulated HSC activation while attenuating oxidative stress, inflammation, and fibrogenesis-related molecular markers.

Free radicals are extremely reactive chemicals that are produced by the liver. Free radicals alter the cell membrane's permeability by forming a covalent bond with the lipids in the membrane,

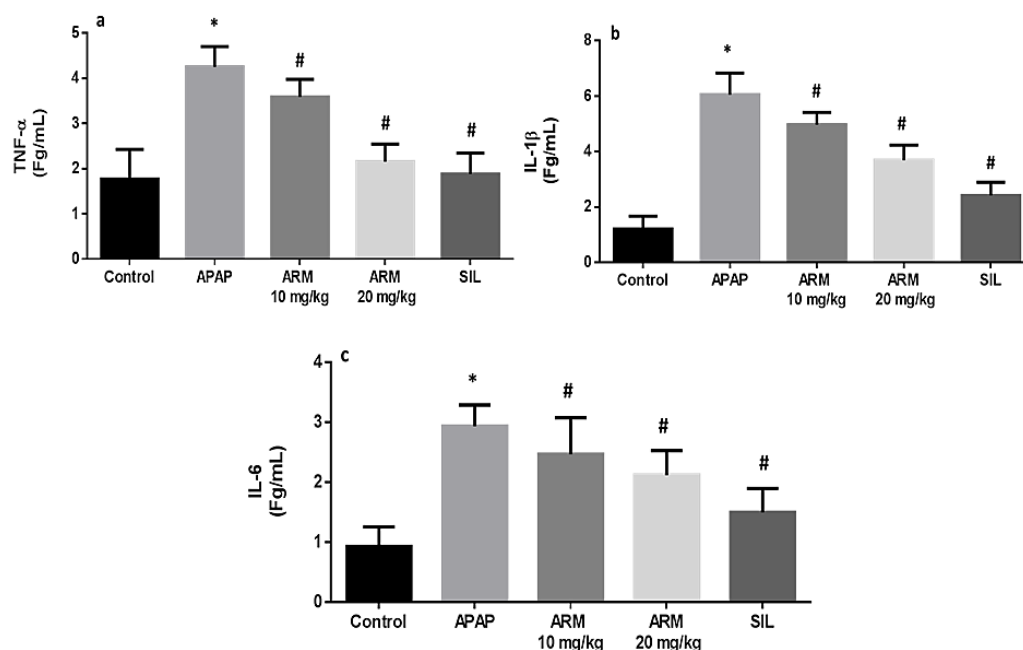


Figure 5: Effects of Armepravine (ARM) (10 and 20 mg/kg) hepatic concentrations of inflammatory Biomarkers.. (a) TNF- α (Fg/mL), (b) IL-1 β (Fg/mL) and (c) IL-6 (Fg/mL) respectively in APAP-exposed Wistar rats. Each point represents the mean $\pm$ SD of six rats. * Significant difference compared with the control group ($p < 0.05$). # Significant difference compared with the Acetaminophen (APAP) group ($p < 0.05$).

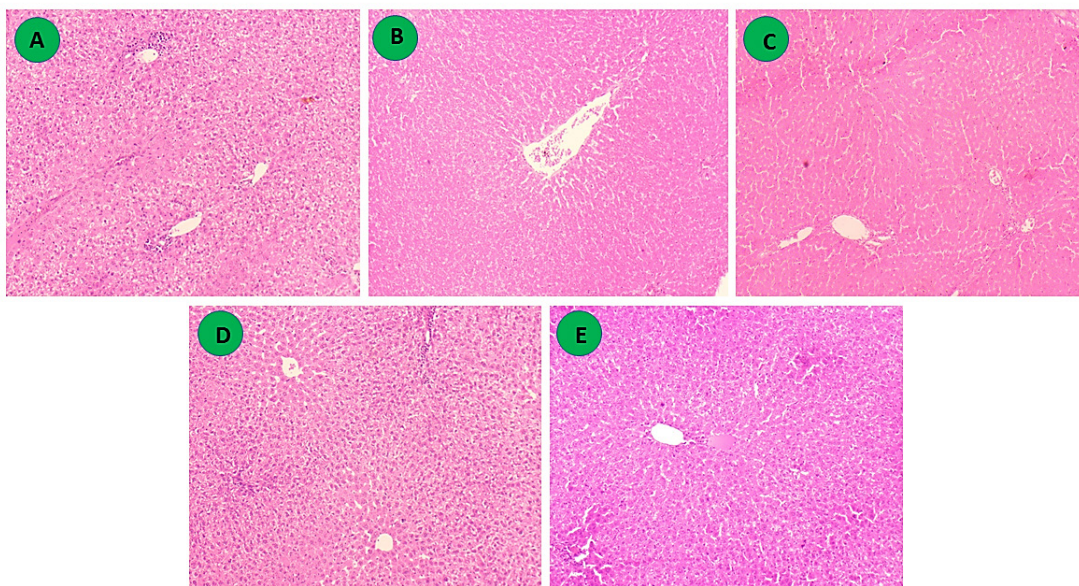


Figure 6: Histopathological changes in the liver after being treated with APAP and/or Armepavine (ARM). A: Normal liver section from control rat shows no histopathological alteration and the normal histological structure of the central vein and surrounding hepatocytes. B: APAP-treated rats showed severe congestion and dilatation in the portal vein associated with inflammatory cell infiltration and edema in the periductal tissue surrounding the cystic dilated bile ducts. C: APAP+ARM 10 mg/kg treated rats, showed congestion in the portal vein associated with few inflammatory cells infiltration surrounding the bile ducts. D: APAP+ARM 20 mg/kg treated rats, there was no histopathological alterations were recorded (H and E). E: (APAP+SIL) received Silymarin positive control (100 mg/kg bwt).

which causes tissue damage.² The production of free radicals and oxidative stress caused by acetaminophen may have contributed to the necrosis of hepatocytes in rats treated with the drug, as evidenced by the aggregation loss of nuclei and inflammatory cells.¹⁰ The rats with ARM pretreatment illustrated the remarkable improvement in these histopathologic structures of the APAP-induced rats. The results of histopathological study of liver tissues from experimental group revealed that the ARM pretreatment improved the hepatocellular architecture, demonstrating its hepatoprotective properties.

This findings of this work may have substantial consequences for clinical and nursing practice, particularly in guiding early intervention and supportive care strategies for drug-induced hepatotoxicity. The present work focused on evaluating the hepatoprotective properties of armepavine and understand its underlying mechanisms. The utilization of herbal medicines as an essential component of alternative medicine has gained more interests, with numerous peoples worldwide are directly relying on natural medications for disease management. The current drug agents derived from medicinal plant sources were being crucial for hepatocyte repair and regeneration, therefore being advantageous for the successful treatment of liver diseases.

The findings of this work suggested that armepavine can protect against APAP-induced hepatotoxicity in the experimental rats. The present conclusion can be further validated by an extensive

evaluations of the mechanism of action in similar experiments with human subjects in the future.

CONCLUSION

APAP has become a widely used analgesic and antipyretic, readily available at retail pharmacies and via prescription. Nonetheless, the extensive application of APAP has considerable hazards, particularly its potential for hepatotoxicity, which is a global concern impacting persons. The current findings of this study underscore the armepavine's exceptional capacity as a potent antioxidant in mitigating drug-induced hepatotoxicity. This APAP-induced liver injury demonstrates the capacity of armepavine to successfully combat oxidative stress in rat model. The study demonstrates a substantial correlation between elevated levels of antioxidant enzymes and a marked decrease in oxidative stress indicators in the armepavine-pretreated rats, highlighting their involvement in combating hepatotoxicity linked to APAP overdose. It significantly diminishes lipid peroxidation, so efficiently regulating free radicals and enhancing the antioxidant defense. The armepavine's preventive properties go marginally beyond the inflammatory suppression. This research offers compelling experimental evidence endorsing the application of armepavine's as a therapeutic agent for liver diseases. Comprehensive understanding of the security profile of the armepavine necessitates future investigations to corroborate these encouraging discoveries, along with further detection of long-term toxicity.

ABBREVIATIONS

AILI: APAP-induced liver injury; **ALF:** Acute Liver Failure; **ALP:** Alkaline phosphatase; **ARM:** Armeapvine; **APAP:** Acetaminophen or N-acetyl-p-aminophenol; **AST:** Aspartate transaminase; **CAT:** Catalase; **DILI:** Drug-Induced Liver Injury; **GSH:** Glutathione; **H₂O₂:** Hydrogen Peroxidase; **IL:** Interleukin; **LPO:** Lipid Peroxidation; **MDA:** Malondialdehyde; **NO:** Nitric Oxide; **PUFA:** Polyunsaturated fatty acid; **ROS:** Reactive oxygen species; **SIL:** Silymarin; **SOD:** Superoxide dismutase; **TBARS:** Thiobarbituric acid reactive substances; **TNF- α :** Tumor necrosis factor-alpha.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

This study is approved by the Ethics Committee of Shanxi Bethune Hospital (Approval Number: YXLL-2024-266).

SUMMARY

The findings from this study suggest that armeapvine is a promising means of reducing liver damage caused by the APAP of Wistar rat. By reducing oxidative stress and reducing inflammation, armeapvine shows its ability as a transformative herbal medicine. These results pave the way for future clinical studies and provide hope for innovative treatment options in the fight against liver diseases.

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