Original article

Effects of Pomegranate (*Punica granatum*) Fruit Juice Extract on Abamectin Induced Hepatoxicity in Adult Albino Rats

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ABSTRACT

Background: The improper use and handling of abamectin in agriculture have had major negative effects on human health. As the liver is a key metabolic organ, regular consumption of pesticide residues from fruits and vegetables may increase the risk of hepatotoxicity. This study aimed to evaluate the potential protective effects of pomegranate (*Punica granatum*) fruit juice extract against abamectin-induced hepatotoxicity in adult albino rats.

Subjects and methods: This experimental study was conducted at PGMI and LGH, Lahore, following ethical approvals from PGMI and UHS. The sample size, calculated using the WHO formula with 90% power and 5% significance, included 24 adult albino rats(6 in each group).Twenty-four Wistar albino rats (180–220 g, 6–8 weeks old) were randomly divided into four groups (n=6 each). Group A served as the control, while Groups B, C, and D were experimental. All groups had free access to water and standard rat food. For 30 days, Group B received abamectin (10 mg/kg), Group C received pomegranate extract (1 mg/kg), and Group D received both treatments (10 mg/kg abamectin + 1 mg/kg pomegranate extract) via oral gavage. On day 30, blood samples were collected for liver enzyme analysis (ALT, AST, and ALP). Rats were sacrificed under general anesthesia, and liver samples were preserved in 10% formalin for histological analysis using Masson's trichrome and hematoxylin and eosin staining. Liver histology was assessed for toxicity and protection by measuring Hepatocyte size and central vein diameters, observing liver color changes, and analyzing biochemical markers (ALT, AST, and GPX) to evaluate hepatic damage and antioxidant defense. Data was collected on a predesigned performa and entered in SPSS version 25. One-way ANOVA and Fisher's exact test were used to analyze quantitative and qualitative variables, respectively, with $p \leq 0.05$ considered significant.

Results: Group B showed significantly increased serum ALT and AST levels, which normalized in Groups C and D. Serum glutathione peroxidase levels were reduced in Group B but restored in Group D. Histological analysis of Group B livers revealed increased central vein diameter, degenerated hepatocytes, nuclear pyknosis, cellular steatosis, sinusoidal congestion, inflammatory cell infiltration, and mild to moderate hepatic fibrosis. Group D showed reduced central vein diameter and partial reversal of histological changes, while Group C exhibited normal liver architecture.

Conclusion: Pomegranate juice extract can be used as a very effective dietary supplement to reduce the harmful effects of pesticides such as abamectin.

Keywords:

Pomegranate Fruit Juice extract, Abamectin, Hepatotoxicity, Albino rats

INTRODUCTION

Pesticide poisoning in humans has long been considered a serious public health issue. Over 10,400 pesticides have been licensed globally as of right now. According to reports, two million tons of pesticides are consumed annually worldwide.[1] Over the past few decades, Pakistan has seen a significant growth in the use of pesticides.[2] The most recent years saw the greatest number of new pesticide records in history. They can build up in organisms, linger in soil or water, and contaminate workers and the general public through food, water, or the air.[3] Abamectin is a broad-spectrum insecticide that has been found in animal studies to cause oxidative stress, neurotoxicity, and liver toxicity (hepatotoxicity). In rats exposed to abamectin, there is an increase in reactive oxygen species (ROS) and malondialdehyde levels, along with heightened activity of antioxidant enzymes like catalase and superoxide dismutase.[4] This series of effects can lead to damage in both the liver and kidneys. On the other hand, pomegranate juice, which is rich in polyphenols, has shown protective benefits in animal

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models. It can lower oxidative stress, stabilize liver enzymes, and prevent liver cell death (hepatocyte apoptosis). These results indicate that pomegranate juice may help reduce tissue damage caused by abamectin.[5] Abamectin exposure increases serum total protein, albumin, globulin, urea, and creatinine levels, along with oxidative stress markers (SOD, MDA, CAT, GPx), while reducing GST and GSH in the liver and brain. Elevated ROS detoxification enzymes (SOD, CAT, GPx) indicate oxidative damage. In Pakistan, pesticide workers show significantly higher liver enzyme levels (ALP, AST, ALT), highlighting occupational health risks.).[6]

Pomegranate (*Punica granatum* L) has long been used to treat ulcers, diarrhea, and male infertility, with increasing evidence supporting its broad pharmacological effects, including anti-diabetic, anti-tumor, anti-inflammatory, anti-fibrotic, and anti-microbial properties.[7]

Literature showed that the female Wistar rats exposed to abamectin inhalation (5.04 mg/L/1 hr daily for 1 week) showed reduced body weight gain and liver weight.[8] Oral abamectin (2 mg/kg, 1/5 LD50) for 5 days in male rats increased TNF-α, oxidative stress, and brain dysfunction. Prenatal/juvenile pesticide exposure was linked to cognitive decline, hyperactivity, and autism spectrum disorders.[9] Pomegranate's bioactive compounds, including polyphenols and punicalagins, offer antioxidant protection, potentially counteracting abamectin-induced hepatotoxicity[10] Pomegranate juice extract improved lipid profiles and prevented lipid accumulation in obese rats.[11] The rationale for the current study is to explore the potential protective effects of pomegranate fruit juice extract in adult male Albino rats against oxidative stress induced by Abamectin administration. This study explores the protective effects of pomegranate juice extract against abamectin-induced oxidative stress in adult male albino rats. Rich in antioxidants, polyphenols, and flavonoids, pomegranate may mitigate liver damage by counteracting oxidative stress and inflammation. Given the widespread use of abamectin in agriculture and its hepatotoxic risks through pesticide residues, identifying natural protective agents is crucial for reducing its harmful effects.

SUBJECTS AND METHODS

An experimental animal study was conducted at the Animal House and Histology Laboratory of the Postgraduate Medical Institute (PGMI), Lahore from Jan-March 2022 to investigate histological changes in the liver of adult male albino Wistar rats after getting the ethical approval. The therapeutic agents used were abamectin and pomegranate fruit juice extract. The sample size, calculated using the WHO formula with 90% power and 5% significance. Twenty-four adult male albino Wistar rats were divided into four groups of 6 each, average weight180-220g, acquired from the Veterinary Research Institute, Lahore were included in current study after all the diseased and female rats were excluded. All animals were acclimatized for one week in a climate-controlled environment at 28.0 ± 2.0°C and 60 ± 10% humidity, with a 12-hour light/dark cycle, standard rat diet, and ad libitum water. The rats were housed separately in cages with appropriate bedding to absorb urine and feces. Each animal was handled and treated according to the guidelines recommended by the Canadian Council of Animal Care.[12] Following acclimatization, a computer-generated random number table was used to randomly assign the rats into four groups (A, B, C, and D), each consisting of six rats. For 30 days, Group A, the control group, was given 1 milliliter of distilled water every day along with regular rat food. For 30 days, Group B, the experimental group, was given oral gavages of abamectin at a dose of 10 mg/kg body weight. For 30 days, Group C was given an oral gavage of pomegranate fruit juice extract at a dose of 1 mg/kg body weight. Group D, which was likewise an experimental group, was given 1 mg/kg body weight of pomegranate extract and 10 mg/kg body weight of abamectin . In each group treatment was given orally by gavage method once a day for 30 consecutive days.

Abamectin was sourced from Syngenta Agro Company, Switzerland, weighed using an electronic scale, and dissolved in distilled water. Pomegranate fruits were purchased from the local market in Lahore, manually peeled, and juiced using a manual press machine. The juice was then concentrated using a vacuum drying oven at 40°C under reduced pressure until a residue remained. The extract was prepared at PCSIR Labs Complex, Lahore. Abamectin LD50 is 1000 mg/kg b.w.; 1/10th of this dose (10 mg/kg b.w.) was used. For a 200 g rat, the required dose was 10 mg, adjusted for weights ranging from 180–200 g. Abamectin (20% solution) contains 200 mg/ml; appropriate dilutions were made.[13] For pomegranate, a dose of 200 mg/kg b.w. was used, equating to 1 mg for a 200 g rat.[14] The experiment lasted 30 days, with all rats sacrificed 24 hours after the final dose. The animals were weighed at the start and end of the experiment using an electronic scale. Blood samples were taken through cardiac puncture before rat was anaesthetized. The rat was anesthetized using chloroform and immediately placed supine on a dissection board. A vertical and horizontal incision was made to expose the liver, which was carefully dissected, washed with saline, blotted, and weighed. The liver was processed in an automatic tissue processor, embedded in paraffin, and preserved in 10% neutral formalin for 72 hours. A rotary microtome was used to cut sections that were 3–5 µm thick. The sections

were then placed on slides and stained for histological examination using Hematoxylin and Eosin and Masson's Trichrome stains. A macroscopic examination was performed to check for any gross abnormalities. Kits for serum AST, ALT and ALP were obtained from Human company, in Germany. Tests were performed in the Biochemistry Laboratory of Lahore General Hospital by using Spectra ProXL (automatic biochemistry analyzer, Diagnostic System GmbH Alte Strasse 9 (Dia Sys, Germany) Assay Kit).

Liver histology was assessed for toxicity and protection by measuring Hepatocyte size and central vein diameters, observing liver color changes, and analyzing biochemical markers (ALT, AST, and GPX) to evaluate hepatic damage and antioxidant defense. Hepatocyte size was measured at 400x magnification, selecting cells with clear boundaries and nuclei. Central vein diameter was assessed at 100x magnification, choosing veins with defined edges. Liver color was assessed under a dissecting microscope and categorized as normal (reddish-brown, coded as "0") or abnormal (pale, coded as "1"). Biochemical parameters, including liver enzyme levels, were analyzed to assess oxidative stress and hepatocellular damage. Data was collected on a predesigned performa .Data were analyzed through SPSS version 25. Mean ± standard deviation was given for quantitative variables i.e., animal body weight, serum levels of ALT, AST and Glutathione peroxidase. Categorical variables i.e. gross appearance of liver (color and surface), nuclear pyknosis in hepatocyte, steatosis, sinusoidal congestion, perivenular fibrosis, inflammatory cells in portal triad were presented in frequency and percentage. Shapiro Wilk's test was used for normality of assessment of data. One-way ANOVA was applied to determine the mean difference in quantitative variable among the groups. Fisher's exact test was used to compare the qualitative variable among the groups. A *p*-value ≤ 0.05 was taken as significant.

RESULTS

The mean body weight of the groups at the beginning of the trial did not differ significantly, according to the data (p-value = 0.377). At the conclusion of the experiment, however, a significant difference in the mean body weight between the groups was noted (p-value = 0.001) (Table. 1).

The liver color remained normal in all sacrificed rats of Groups A, C, and D (100%), while one rat's liver in Group B (16.7%) exhibited abnormal coloration; however, the difference was not statistically significant (p > 0.999). The hepatocyte size was significantly increased in Group B (30.7 ± 2.8 µm) compared to the other groups, which had similar diameters (19.5–20.7 µm, p-value <0.001). Similarly, the diameter of the central vein was markedly larger in Group B (60.4 ± 3.0 µm) compared to the other groups (20.3–20.8 µm, p-value <0.001). Nuclear pyknosis, an indicator of cellular damage, was absent in Groups A, C, and D (100%), but was present in all animals of Group B (100%), with this difference being statistically significant (p-value <0.001). These findings suggest that abamectin exposure (Group B) causes significant histological alterations in the liver, which were mitigated by pomegranate co-administration (Group D) (Table 2).

Table 1: Comparison of initial body weight and final body weight among groups

Variables	Group A (Control)	Group B (Abamectin)	Group C (Pomegranate)	Group D (Abamectin + Pomegranate)	p-value
Mean weight of the rats at the start of experiment(g)	200.5 ± 3.1	201.7 ± 2.3	199.3 ± 3.3	202.0 ± 2.6	0.377
Mean weight of the rats at the end of experiment(g)	208.3 ± 2.4	197.20 ± 1.4	208.2 ± 2.6	210.3 ± 2.3	0.001*

Table 2: Comparison of histological parameters of liver among groups

Variables	Group A (Control)	Group B (Abamectin)	Group C (Pomegranate)	Group D (Abamectin + Pomegranate)	p-value
Color of Liver					
Normal	6 (100%)	5 (83.3%)	6 (100%)	6 (100%)	> 0.999
Abnormal	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	
Diameter of Hepatocyte (µm)	19.5 ± 1.4	30.7 ± 2.8	19.7 ± 1.4	20.7 ± 1.2	<0.001
Diameter of Central Vein (µm)	20.7 ± 1.1	60.4 ± 3.0	20.8 ± 2.0	20.3 ± 1.5	<0.001
Nuclear pyknosis in hepatocytes					
Absent	6 (100%)	0 (0%)	6 (100%)	6 (100%)	<0.001
Present	0 (0%)	6 (100%)	0 (0%)	0 (0%)	

Fisher's Exact Test

Table 3: Comparison of biochemical parameters among groups

Variables	Group A (Control)	Group B (Abamectin)	Group C (Pomegranate)	Group D (Abamectin + Pomegranate)	p-value
ALT (U/L)	25.3 ± 2.0	123.5 ± 4.2	26.3 ± 1.3	70.8 ± 2.7	<0.001*
AST (U/L)	46.9 ± 2.8	138.5 ± 7.3	47.9 ± 2.7	88.1 ± 3.0	<0.001*
GPx levels (U/L)	55.8 ± 5.9	40.1 ± 3.0	101.4 ± 7.4	54.4 ± 7.1	<0.001*

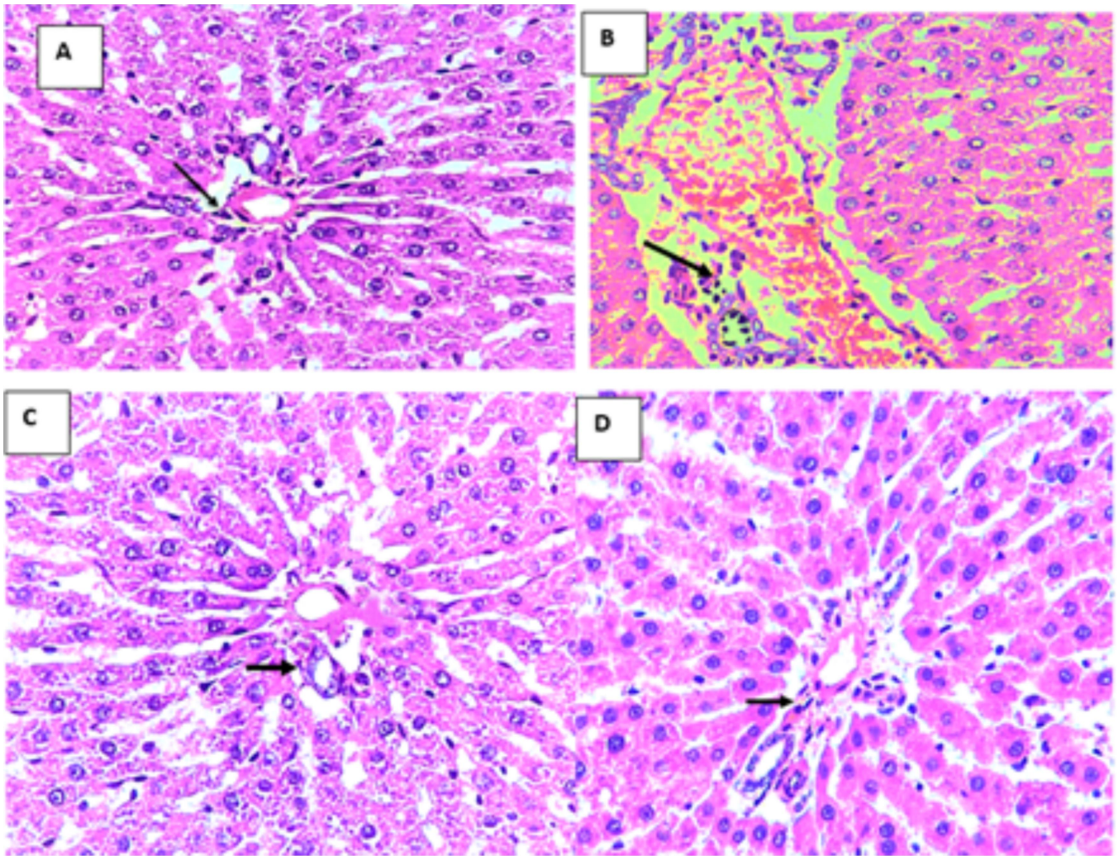

Figure 1: A: Photomicrograph of rat liver (Control Group-A) showing mild portal inflammation (black arrow) **B:** Rat liver (Experimental Group-B) showing moderate portal inflammation (black arrow). **C:** Rat liver (Experimental Group-C) showing mild portal inflammation (black arrow). **D:** Rat liver (Experimental Group-D) showing mild portal inflammation (black arrow), H&E stain, 400x.

Alanine aminotransferase (ALT) levels were significantly elevated in Group B (123.5 ± 4.2 U/L) compared to the control (Group A: 25.3 ± 2.0 U/L), pomegranate-only (Group C: 26.3 ± 1.3 U/L), and combined treatment groups (Group D: 70.8 ± 2.7 U/L), with a statistically significant difference (p-value <0.001). Similarly, aspartate aminotransferase (AST) levels were markedly higher in Group B (138.5 ± 7.3 U/L) than in Groups A (46.9 ± 2.8 U/L), C (47.9 ± 2.7 U/L), and D (88.1 ± 3.0 U/L), also with p-value <0.001. Glutathione peroxidase (GPx) levels were significantly reduced in Group B (40.1 ± 3.0 U/L) compared to Group A (55.8 ± 5.9 U/L) and Group D (54.4 ± 7.1 U/L). However, Group C showed a substantial increase in GPx levels (101.4 ± 7.4 U/L), highlighting the antioxidant effect of pomegranate. These findings indicate that abamectin exposure significantly impairs liver function and antioxidant defenses, while pomegranate supplementation alone or in combination mitigates these effects (Table 3).

DISCUSSION

This study showed statistically significant results manifested by gross changes in adult albino rats' body weight, liver weight, diameter of hepatocyte and central vein, serum levels of ALT, AST and GPx. Architecture of hepatocyte, sinusoidal congestion, portal triad inflammation and hepatic fibrosis revealed statistically significant results. In the beginning of the investigation, the mean animal body weight of all four groups in the current study was statistically insignificant; nevertheless, by the conclusion of the trial, there was a statistically significant difference (p-value = 0.377 and 0.001) between groups. At the conclusion of the experiment, group B's mean weight was substantially lower than that of groups A and D, respectively, compared to groups C and D, respectively. These findings were comparable with another study reported that pomegranate leaf extract led to the highest weight loss, reducing body weight by 10.44%, indicating its potential anti-obesity properties. Similarly, pomegranate peel extract showed a 9.4% reduction, suggesting beneficial effects on weight management.[15] This showed that the mean weight of abamectin-treated rats is significantly less (p-value <0.05). Weight reduction was due to the suppression of appetite along with free radicals which strike electrons in cell membranes leading to oxidative degeneration of lipids.[16]

The results were similar to those published by Disner and colleagues.[3] A contradictory report was stated by Khizomy and associates.[17] Maintenance of body weight in group D is due to its membrane-stabilizing effects inhibiting action on ROS-producing enzymes. It revealed the possible protective role of pomegranate fruit juice extract against abamectin induced hepatotoxicity.[18,19] There was statistically insignificant change in the color and surface of the liver among all study groups. It remained reddish brown as normal and smooth respectively., The results are correlated with studies documented by Elhosary in 2018.[20] In present study, histological examination of the liver preparation manifested the nuclear pyknosis in hepatocytes as signs of hepatic toxicity in experimental Group B treated with abamectin Pyknotic nuclei seen in hepatocytes of abamectin treated group B was due to reactive oxygen species produced as a result of necrosis mostly characterized by pyknosis. These findings are in accordance with work carried out by Mansour and coresearchers.[21] The animals of control group A and group C treated with pomegranate fruit juice extract of current study showed normal hepatic cells with no pyknosis. Group D demonstrated that treatment with pomegranate juice extract along with abamectin mitigated the oxidative stress induced by abamectin exposure and alleviated the lesions caused by abamectin toxicity in rats, and significantly (p-value <0.05) reversed the abamectin-induced changes. In group D pomegranate fruit juice extract showed marked amelioration and restoration due to its antioxidant property protecting hepatocytes as described in an earlier study.[22] Pomegranate fruit juice extract have been reported to be a good source of phenolic and flavonoid compounds which act as strong antioxidants by scavenging the free radicals and preventing their accumulation in liver. Same results were shown in a previous study.[23] Study revealed significantly elevated serum ALT and AST levels in the abamectin-treated Group B compared to Groups A, C, and D (p-value <0.001). Reactive oxygen species production and lipid peroxidation likely contributed to this elevation. These findings align with other studies, which reported increased ALT, AST, and ALP levels in abamectin-treated rats.[21,22] Similar results were reported by Zeinali and coworkers.[24] This study has limitation for a small sample size and funding constraints. Further research on plant-based dietary supplements with detoxifying properties is recommended, alongside precautionary measures for pesticide use by farmers.

CONCLUSION

Pomegranate juice may have protective role against hepatotoxicity induced by abamectin. Given the increasing prevalence of insecticide toxicity due to the use of pesticides such as abamectin, pomegranate juice may be considered for human studies to confirm its hepatoprotective role and treatment against abamectin-induced liver damage.

Author Contributions

SAW: Conceptualization, manuscript drafting, data Collection and manuscript editing, editing and revision of manuscript.
SG: Conceptualization, manuscript drafting, final review.
MY: Data Analysis, drafting the manuscript, editing and revision of manuscript, final approval.

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