



HEPATOPROTECTIVE EFFECTS OF *PUNICA GRANATUM* FRUIT EXTRACT AGAINST SODIUM BENZOATE-INDUCED LIVER INJURY IN SWISS MICE

Godspower Micheal¹, Eme Efioanwan Orlu², Adetutu Olubunmi Obulor^{*3}

^{1,2,3}Rivers State University.



***Corresponding Author: Adetutu Olubunmi Obulor**

Rivers State University.

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1. ABSTRACT

Sodium benzoate is a widely used food preservative; however, prolonged exposure has been associated with oxidative stress and liver dysfunction. This study investigated the hepatoprotective effects of *Punica granatum* against sodium benzoate-induced liver injury in Swiss mice. Thirty adult Swiss mice were randomly assigned into six groups: Group A (control), Group B (40 mg/kg body weight/day sodium benzoate), Group C (20 mg/kg body weight/day sodium benzoate), Group D (250 mg/kg body weight/day *Punica granatum*), Group E (40 mg/kg body weight/day sodium benzoate + 250 mg/kg body weight/day *Punica granatum*), and Group F (20 mg/kg body weight/day sodium benzoate + 250 mg/kg body weight/day *Punica granatum*). Following a 35-day treatment period, blood samples were collected by ocular puncture for the determination of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH). Liver tissues were processed for histopathological examination. Data were analyzed using one-way ANOVA. Results showed significant increase ($p < 0.05$) in AST, ALT, ALP, GGT, and LDH activities in sodium benzoate-treated groups compared with the control, indicating hepatic injury. However, mice treated with *Punica granatum* alone exhibited enzyme levels comparable to the control group. Histopathological evaluation revealed normal hepatic architecture in the control and *Punica granatum*-treated groups, whereas sodium benzoate exposure caused hepatocyte degeneration, cytoplasmic vacuolation, apoptosis, and distortion of liver architecture. Co-administration of *Punica granatum* significantly ameliorated these biochemical and histological alterations. In conclusion, *Punica granatum* exhibited marked hepatoprotective effects against sodium benzoate-induced liver toxicity and may serve as a promising natural agent for the prevention of preservative-associated hepatic damage.

KEYWORDS: Sodium benzoate, *Punica granatum*, hepatotoxicity, liver enzymes, histopathology, Swiss mice.

2. INTRODUCTION

The increasing demand for convenience foods resulting from rapid technological advancement and modern lifestyles has led to a substantial rise in the consumption of processed and prepackaged food products. To maintain product quality, safety, and shelf life, food manufacturers commonly incorporate additives such as preservatives, colorants, flavor enhancers, and antioxidants. Food preservatives play an important role in preventing microbial growth, reducing spoilage, and extending the storage stability of food products. However, growing concerns have emerged regarding the

potential health effects associated with prolonged exposure to some synthetic preservatives.

Sodium benzoate (E211) is one of the most widely used food preservatives in beverages, fruit juices, sauces, and other processed foods because of its effective antimicrobial properties under acidic conditions. Although regulatory agencies consider sodium benzoate safe within recommended limits, increasing experimental evidence suggests that excessive or prolonged consumption may adversely affect physiological functions. Studies have shown that sodium benzoate can induce oxidative stress, cellular injury, and organ

toxicity^[1,2] particularly in the liver, which serves as the principal organ for the metabolism and detoxification of xenobiotics.^[3] reported that sodium benzoate administration induced oxidative stress and tissue damage in experimental animals, highlighting concerns about its long-term safety.

The liver is highly vulnerable to toxic insults because it is directly involved in the metabolism and biotransformation of dietary and environmental chemicals. Hepatotoxicity remains a significant public health concern worldwide, with food additives among the factors implicated in liver dysfunction. Exposure to sodium benzoate has been associated with elevated serum activities of liver injury biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP), indicating hepatocellular damage. These biochemical alterations are frequently accompanied by histopathological changes including hepatocyte degeneration, inflammation, necrosis, and disruption of normal hepatic architecture. Previous studies have demonstrated that oxidative stress and inflammatory responses are central mechanisms underlying sodium benzoate-induced liver injury.^[2,4]

The search for safer and more effective approaches to mitigate chemical-induced liver injury has stimulated interest in natural products with antioxidant and anti-inflammatory properties. Medicinal plants and fruits contain numerous bioactive compounds capable of neutralizing reactive oxygen species, enhancing endogenous antioxidant defenses, and protecting tissues against oxidative damage. Several studies have documented the protective effects of plant-derived products against chemically induced hepatotoxicity.^[5,6,7,8] Among these natural products, pomegranate (*Punica granatum* L.) has attracted considerable attention because of its high content of polyphenols, flavonoids, anthocyanins, tannins, and phenolic acids. These phytochemicals possess potent antioxidant and anti-inflammatory activities that contribute to various health benefits. Experimental studies have shown that pomegranate extracts and juice can reduce lipid peroxidation, improve antioxidant status, lower serum liver enzyme activities, and preserve hepatic histoarchitecture in different models of liver injury.^[9,10,11,12,13,14,15,16,17,18,19]

Despite growing evidence supporting the hepatoprotective potential of *Punica granatum*, information regarding its effectiveness against sodium benzoate-induced liver damage remains limited. Therefore, this study was designed to evaluate the effect of *Punica granatum* on liver injury biomarkers and hepatic histoarchitecture in Swiss mice exposed to sodium benzoate.

3. MATERIAL AND METHODS

3.1 Experimental Location

The experiment was conducted at the animal house of the Department of Animal and Environmental Biology of Rivers State University (Coordination 4° 48' 14"N 6° 59' 12"E) between November 2025 and May 2026.

3.2 Experimental Animal care and Management

The animal house was appropriately cleaned, plastic cages were washed with some disinfectants and left to dry with sunlight for 24 hours, drinking cups and food trays were also equally washed well. The rats were kept in plastic cages under standard conditions (12hrs:12hrs) and allowed to acclimatize for 14 days before the commencement of the experiment. Rats were fed standard pellets and clean water was made available to them. All experiments were carried out according to institutional protocols of animal care at Rivers State University, Port Harcourt.

3.3 Preparation of SB and *Punica granatum* fruit extract

Sodium Benzoate (SB) was purchased from a reputable chemical store in Port Harcourt. Dosage used was based on the bodyweight of the animals.

Fresh fruits of *Punica granatum* were purchased in good physiological condition from (Fruit garden) in Rivers State. The fruits were thoroughly washed under running tap water to remove dirt, debris, and potential contaminants. Pure juice (100%) of *Punica granatum* was extracted daily using a juice extractor (Model: Unicam 5625 UV/VIS).

3.4 Study design

A total of 30 adult Swiss mice were randomly divided into six groups (n=5). Group A was the Control, B was administered 40mg/kg/bw/day of sodium benzoate (SB) only, C was administered 20mg/kg/bw/day of SB only, D was administered 250 mg/kg/bw/day of 100% *Punica granatum* fruit extract only, E was administered 40mg/kg/bw/day of SB+ 250 mg/kg/bw/day of 100% *Punica granatum* fruit extract, F was administered 20mg/kg/bw/day of SB+ 250 mg/kg/bw/day of 100% *Punica granatum* fruit extract.

3.5. Biochemical Analysis

Serum activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and lactate dehydrogenase (LDH) were determined using commercially available diagnostic kits according to the manufacturer's instructions. Serum was obtained following centrifugation of whole blood at 2500 rpm for 10 min and stored at -20°C until analysis.^[20]

3.6. Histopathological analysis of the Liver

Known weight (0.5g) of the liver was fixed in 100% neutral formalin which were dehydrated through ascending grades of ethanol (70, 90, 95% v/v). They

were cleaned in xylene then impregnated and embedded in paraffin wax and sectioned with a digital microtome at 5 μ m thick. Slides were stained with Hematoxylin and Eosin (H&E) stains and was viewed with a digital microscope Biosphere Miller B with an image processor DN2- Microscopy image processing software at X400 magnification

3.7 Data analysis

The experimental data were subjected to one-way Anova, where significant differences are found, pair wise comparisons using Turkey test, using the JAPS software version 0.93.0. Significance level set at $p < 0.05$.

4. RESULT

Liver enzymes

Fig 1 shows AST levels varied significantly across all treatment groups. Group (A) recorded an AST value of 39.40 ± 1.14 U/L. In group (B), AST value was 62.40 ± 2.07 U/L, while a further increase was observed in the 20 mg/kg group (C) with an AST value of 71.40 ± 1.14 U/L. Mice treated with *Punica granatum* only (Group D) recorded AST activity of 43.40 ± 3.97 U/L, slightly higher than the control but far below the sodium benzoate groups. Co-administration of *Punica granatum* with sodium benzoate produced mixed outcomes. The 40 mg/kg sodium benzoate + *Punica granatum* group (E) recorded high AST activity (69.20 ± 1.79 U/L). However, a significant protective effect was evident in the 20 mg/kg sodium benzoate + *Punica granatum* group (F), where AST decreased significantly to 26.20 ± 1.92 U/L, a value significantly lower than the control.

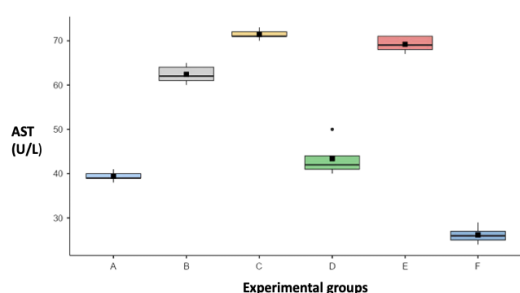


Fig. 1: SB and Punicagranatum co-treatment on serum AST level.

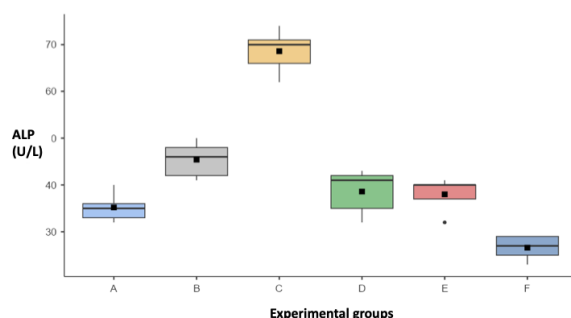


Fig. 3: SB and Punicagranatum co-treatment on serum ALP level.

In fig 2, group A recorded ALT value of 26.60 ± 1.34 U/L. Administration of sodium benzoate alone (B and C) caused a substantial and dose-dependent increase in ALT activity. ALT significantly increased to 54.60 ± 2.70 U/L (group B) and 75.80 ± 0.84 U/L in group C. Mice treated with *Punica granatum* only (Group D) showed moderately elevated ALT levels (34.80 ± 1.92 U/L), with values close to control. Co-administration of *Punica granatum* with sodium benzoate resulted in partial amelioration of liver injury. In Group E, ALT decreased to 58.40 ± 7.44 U/L and 31.20 ± 3.70 U/L in group F. In fig 3, group A recorded a mean ALP value of 35.20 ± 3.11 U/L which significantly increased in group B and C with 45.40 ± 3.85 U/L and 68.60 ± 4.67 U/L respectively. *Punica granatum* alone (Group D) produced a mild increase in ALP (38.60 ± 4.83 U/L) compared to the control, though the change was relatively non-significant. In Group E (40 mg/kg sodium benzoate + *Punica granatum*), ALP decreased to 38.00 ± 3.67 U/L, contrasting with the elevation observed in sodium-benzoate-only groups. Notably, the 20 mg/kg sodium benzoate + *Punica granatum* group (Group F) demonstrated the lowest ALP value among all groups (26.60 ± 2.61 U/L).

The serum γ -glutamyl transferase (GGT) activity of mice in the different treatment groups is presented in fig 4. Group A recorded GGT mean value of 34.00 ± 1.00 U/L. Animals in group B showed a significant increased GGT level of 42.60 ± 1.52 U/L and 50.60 ± 1.52 U/L in group C. *Punica granatum* alone (Group D) recorded 36.60 ± 1.14 U/L and 49.40 ± 1.82 U/L) in group E while a significant decrease was recorded in group F with 22.20 ± 2.17 U/L which was the least value among the group.

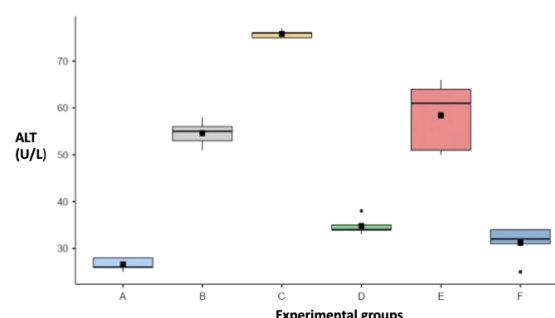


Fig. 2: SB and Punicagranatum co-treatment on serum ALT level.

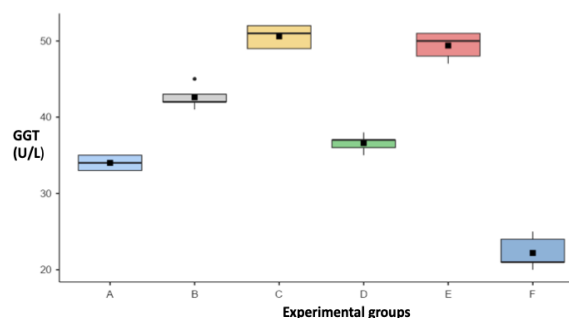


Fig. 4: SB and Punicagranatum co-treatment on serum GGT level.

Liver Histopathology

Fig 5 shows the histopathological micrograph of Swiss mice from the control group (Group A). The normal architectural structure of the liver is shown with normal hepatocytes, central vein and uncongested sinusoids. The liver epithelium of group B animals is shown in fig 6. There was massive degeneration of the hepatocytes resulting in distortion of the normal architecture of the liver epithelium. The epithelium became vacuolated with apoptotic cells, congestion of the central portal vein as well as sinusoids, several binucleated hepatocytes, and aggregation of inflammatory cells were observed.

In fig 7, liver micrograph from group C. reveals hepatocytes degeneration, infiltration of the central portal vein by the lymphocytes and hepatocyte vacuolation, binucleated and apoptotic cells while group D shows a normal liver epithelium with standard hepatocyte

architecture comparable to the control group (fig 8). Fig 9 is the liver epithelium of group E animals showing degeneration of the hepatocytes. The epithelium are vacuolated with apoptotic cells. Some congestion of the central portal vein as well as sinusoidal congestion. Observed were numerous binucleated hepatocytes. However, the entire hepatocytes appeared to be undergoing accelerated mitotic division based on the number of mitotic figures observed.

Close observation of group F reveals an epithelium undergoing recovery. Most of the dividing hepatocytes are at late stage and numerous ones completing cell division. The architecture of the liver epithelium was not distorted although some vacuolations were still observed but no aggregation of inflammatory hepatocytes. The epithelium appears to be undergoing full recovery (fig 10).

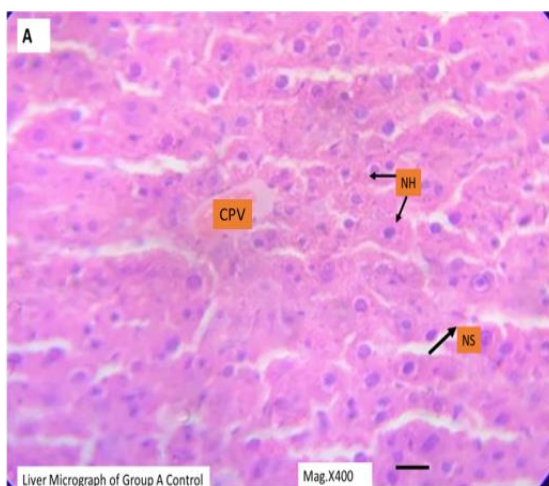


Fig 5 CPV-Central Portal Vein, NH-Normal Hepatocytes, NS-Normal Liver Sinusoids.

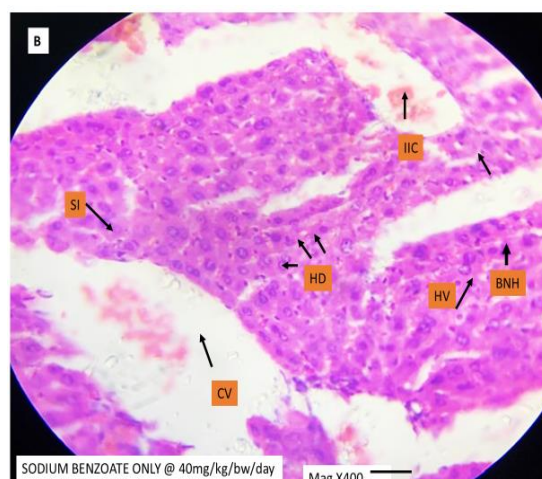


Fig. 6: CV Cytoplasmic vacuolation, HD Hepatocyte Degeneration, IIC Infiltration of inflammatory cells, HV Hepatocyte vacuolation, BNH, Binucleated hepatocytes, SI Sinusoid infiltration.

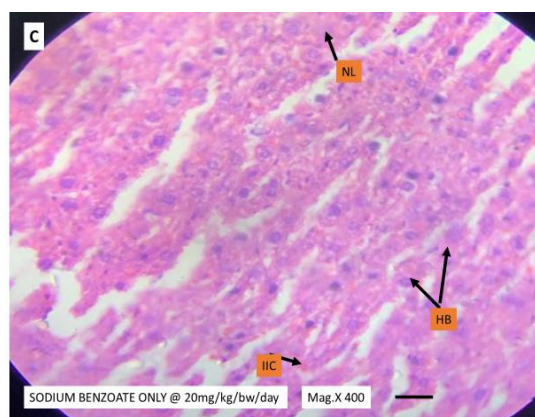


Fig. 7: IIC Infiltration of inflammatory cells, HB Hepatocyte ballooning.

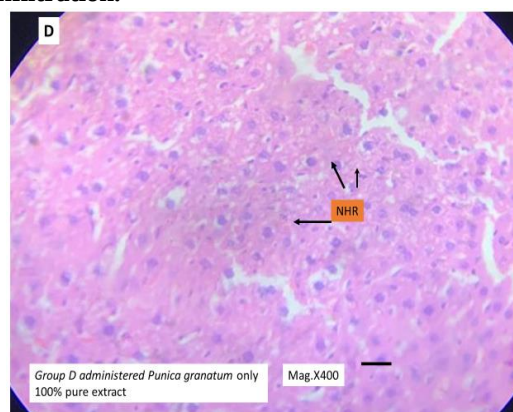


Fig. 8: NHR Normal Hepatocyte regeneration.

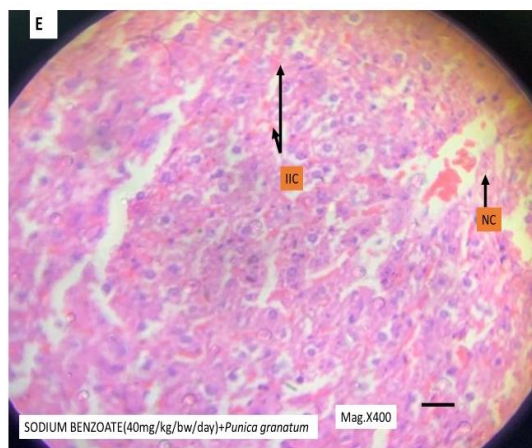


Fig. 9: IIC Infiltration of inflammatory cells, NC Necrotic cell.

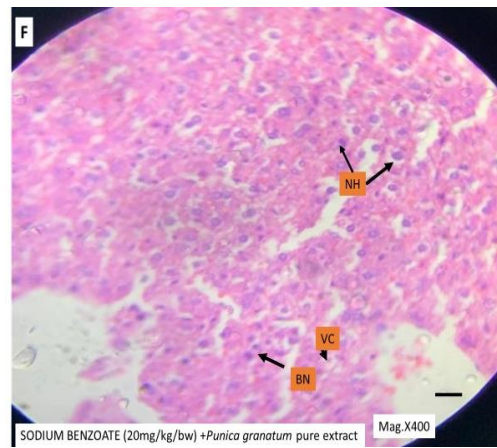


Fig. 10: BN Binucleation NH Normal hepatocytes.

5. DISCUSSION

The present study demonstrated that sodium benzoate exposure induced marked hepatic injury in Swiss mice, as evidenced by significant elevations in serum AST, ALT, ALP, GGT, and LDH activities, accompanied by severe histopathological alterations including hepatocyte degeneration, vacuolation, apoptosis, inflammatory cell infiltration, and vascular congestion. Conversely, administration of *Punica granatum* alone preserved normal hepatic architecture and maintained liver enzyme activities close to control values, while co-administration of *Punica granatum* with sodium benzoate attenuated most of the biochemical and histological abnormalities, particularly in Group F.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are sensitive indicators of hepatocellular damage because they are released into circulation following disruption of hepatocyte membrane integrity. In the present study, sodium benzoate administration significantly increased AST and ALT levels in Groups B and C relative to the control group, indicating substantial hepatocellular injury. Interestingly, the lower-dose sodium benzoate group (C) exhibited higher AST and ALT values than Group B, suggesting severe hepatic stress within the exposure period. Elevated transaminases have been widely associated with sodium benzoate-induced oxidative damage, lipid peroxidation, and cellular membrane disruption in experimental animals. Recent reviews have reported that excessive sodium benzoate exposure adversely affects liver function by increasing serum liver enzymes and inducing histological lesions in hepatic tissue.^[1,2,3,21]

The significant increases observed in alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) further support hepatic dysfunction. ALP and GGT are commonly regarded as markers of biliary injury and impaired hepatobiliary function. The elevated values recorded in sodium benzoate-treated groups suggest disturbances in hepatic secretory processes and possible cholestatic changes. Previous studies have similarly shown that sodium benzoate exposure alters ALP and

GGT activities through oxidative injury and inflammatory responses within hepatic tissues.^[22]

Lactate dehydrogenase (LDH), a non-specific marker of cellular injury and necrosis, was also markedly elevated in Groups B and C. Increased LDH activity reflects leakage of intracellular enzymes from damaged hepatocytes into circulation. The pronounced elevation observed in Group C indicates extensive membrane damage and loss of cellular integrity. Similar increases in LDH have been reported in experimental models of chemically induced hepatotoxicity and are considered evidence of severe tissue injury.^[23]

Administration of *Punica granatum* alone (Group D) produced liver enzyme values comparable to the control group and maintained normal histological architecture. These findings indicate that the extract itself was not hepatotoxic and may possess intrinsic hepatoprotective properties.

The hepatoprotective effect became more evident in the co-treatment groups. Group F (20 mg sodium benzoate + *Punica granatum*) exhibited substantial reductions in AST, ALT, ALP, GGT, and LDH compared with sodium-benzoate-only groups. Remarkably, AST, GGT, and LDH values in Group F were even lower than control values, suggesting a strong protective and restorative effect. Although Group E also showed some improvement relative to sodium benzoate exposure, the protective effect was less pronounced, possibly because the higher sodium benzoate dose generated greater oxidative damage that exceeded the protective capacity of the administered *Punica granatum*.

The observed biochemical improvements may be attributed to the rich phytochemical composition of *Punica granatum*, particularly punicalagins, ellagic acid, anthocyanins, flavonoids, and tannins. Recent evidence indicates that pomegranate supplementation can significantly reduce liver enzyme activities, especially AST, ALT, and GGT, while improving hepatic antioxidant status and reducing inflammation.^[19,24,25]

Liver sections from the control group displayed normal hepatic architecture characterized by well-arranged hepatocytes, intact central veins, and uncongested sinusoids. In contrast, Group B exhibited severe hepatic lesions, including massive hepatocyte degeneration, cytoplasmic vacuolation, apoptotic cells, congestion of the portal vein and sinusoids, inflammatory cell infiltration, and numerous binucleated hepatocytes. Similar but slightly less severe alterations were observed in Group C. The presence of binucleated hepatocytes may represent a compensatory regenerative response of the liver following toxic exposure. Such regenerative changes frequently occur when hepatocytes attempt to replace damaged cells and restore tissue integrity.

Conversely, liver sections from Group D showed normal hepatic organization comparable to the control group, confirming the therapeutic effect of *Punica granatum*. The preservation of hepatocyte morphology and vascular structures suggests that the extract supports hepatic homeostasis and protects against oxidative injury. Previous studies have similarly reported that pomegranate treatment restores normal hepatic architecture, reduces inflammatory infiltration, and prevents hepatocyte degeneration in various experimental models of liver injury.^[12,13,14,16,17,18,24]

6. CONCLUSION

The findings of this study demonstrate that sodium benzoate administration caused significant liver injury in Swiss mice, as evidenced by elevated AST, ALT, ALP, GGT, and LDH activities and severe histopathological alterations including hepatocyte degeneration, vacuolation, apoptosis, inflammatory infiltration, and vascular congestion. Treatment with *Punica granatum* alone maintained normal liver function and hepatic architecture. Co-administration of *Punica granatum* with sodium benzoate markedly ameliorated both biochemical and histological indices of liver damage, with the greatest protection observed in the 20 mg sodium benzoate + *Punica granatum* group (Group F). These results suggest that *Punica granatum* possesses significant hepatoprotective activity against sodium benzoate-induced liver toxicity, likely through its potent antioxidant and anti-inflammatory phytoconstituents, and may serve as a promising natural therapeutic agent for preventing preservative-induced hepatic injury.

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