

Protective Effect of Aspirin Against Gentamicin-Induced Hepatotoxicity in Rats Model

Asmaa Moafa¹, Sara A. Aldossary²,
Mohammed Al Mohaini³ and Abdulkhaliq J. Alsalman⁴

¹Pharmacy Services Department, Johns Hopkins Aramco Healthcare (JHAH), Saudi Arabia.

²Department of Pharmaceutical Sciences, College of Clinical Pharmacy,
King Faisal University, 31982 Alahsa, Saudi Arabia.

³Basic Sciences Department, College of Applied Medical Sciences, King Saud bin Abdulaziz
University for Health Sciences, King Abdullah International Medical Research Center,
Alahsa 31982, Saudi Arabia.

⁴Department of Clinical Pharmacy, Faculty of Pharmacy,
Northern Border University, Rafha 91911, Saudi Arabia.

*Corresponding Author E mail: saldossary@kfu.edu.sa

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Gentamicin is an extensively used antibiotic with potent antimicrobial exertion, but its clinical mileage is limited by its eventuality to induce hepatotoxicity. This study aimed to probe the defensive effect of aspirin against gentamicin-convinced hepatotoxicity in a rat model. Adult manly Wistar rats were divided into four groups control, aspirin, gentamicin, and aspirin- gentamicin. The creatures were treated for 15 successive days, and colorful biochemical parameters were estimated. Pre-treatment with aspirin significantly downgraded the adverse goods of gentamicin on liver weight. It also eased the elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) situations, indicating the preservation of liver function. Aspirin treatment suppressed hepatic lipid peroxidation, as substantiated by a reduction in malondialdehyde (MDA) situations. likewise, it averted the reduction of glutathione (GSH) situations and catalase exertion convinced by gentamicin administration. These findings suggest that aspirin exerts a hepatoprotective effect by reducing oxidative stress and enhancing antioxidant defense mechanisms. The protective mechanisms of aspirin may involve its anti-inflammatory properties, as well as its antioxidant effects. Aspirin has the potential to inhibit inflammation-induced liver injury and modulate signaling pathways involved in cell survival and apoptosis. However, further investigations are needed to elucidate the precise molecular mechanisms underlying its protective effects. Overall, pre-treatment with aspirin demonstrated a protective effect against gentamicin-induced hepatotoxicity in this rat model. It mitigated liver damage, preserved liver function, and enhanced antioxidant defense mechanisms. These findings suggest that aspirin could be a potential therapeutic agent for the prevention and management of drug-induced liver injury. Further studies, including clinical trials, are necessary to determine the optimal dosage, duration, and safety profile of aspirin in humans.

Keywords: Aspirin, Gentamicin, Hepatotoxicity, and rats.

The use of certain medications, while beneficial for treating various conditions, can sometimes lead to adverse effects on the liver.

Gentamicin, a widely used antibiotic, has been associated with hepatotoxicity, which refers to liver damage caused by toxic substances. In recent

years, research has focused on exploring potential protective agents that can mitigate the hepatotoxic effects of gentamicin. One such agent of interest is aspirin, a commonly used medication with known anti-inflammatory and antioxidant properties¹.

Gentamicin-induced hepatotoxicity is characterized by liver dysfunction, increased liver weight, and an increase in liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), in the serum. Hepatic lipid peroxidation, reduction in the level of antioxidants, and impairment of cellular functions contribute to the development of gentamicin-induced liver injury. Aspirin, also known as acetylsalicylic acid, has been investigated for its potential hepatoprotective properties. Studies have suggested that aspirin possesses antioxidant and anti-inflammatory properties, which may help alleviate liver damage induced by gentamicin²⁻⁴. The mechanism underlying the protective effect of aspirin is believed to involve the inhibition of oxidative stress and the modulation of inflammatory pathways.

The goal of this study was to examine the effect of aspirin on gentamicin-induced hepatotoxicity in an animal model. Specifically, we examined the impact of aspirin on liver weight, serum liver enzymes (ALT and AST), as well as oxidative stress markers, such as malondialdehyde (MDA), glutathione (GSH), nitric oxide (NO), and catalase activity. Male Wistar rats were randomly grouped into four: control, aspirin group, gentamicin group, and aspirin-gentamicin group⁵. The animals were treated according to the designated groups, and liver weight, serum liver enzymes, and oxidative stress markers were assessed during the experimental time. The doses of gentamicin and aspirin were chosen to depend on previous studies⁶⁻⁷.

MATERIAL AND METHOD

Drugs

Gentamicin (CAS- No 1405410, 100 pure) and aspirin (CAS- No 502658 chastity 98) were purchased from Sigma- Aldrich Chemical Company (St.Louis, Missouri, USA). Other reagents were of logical grade.

Animals

Wistar rats (70 – 80 days old) importing

were selected (Faculty of Pharmacy, King Faisal University,), housed in clean polypropylene coops, and maintained on a 12- hour light/ dark cycle at a temperature of 20 – 25C with ad libitum access to standard food and water.7 days pre-experimental rats were handled daily for minimize their physiological responses to handling for posterior protocols. All treatment described was performed according to the Research Ethics Committee of King Faisal University.

Experimental protocol

Animals were sectioned into four groups consisting of six rats each. Group I(control) entered the vehicle. Group II (aspirin group) entered aspirin 10mg/ ml (200mg/ kg/ day intragastrical). Group III (gentamicin group) was treated with gentamicin (100 mg/ kg/ day by intraperitoneal) in a single injection. Group IV (aspirin- gentamicin group) was treated with aspirin and gentamicin by the same schedule. Groups II and IV entered aspirin from day 1 until day 15(the total period of the trial). Groups III and IV entered gentamicin for 10 successive days, starting from the sixth day of the trial until day 15. The selected doses of gentamicin and aspirin were chosen based on previous studies⁷.

Sample medication and biochemical tests

Animals were killed by stunning and cervical dislocation under Schedule 1 according to the United Kingdom Animals (Scientific Procedures) Act 1986 a day after the last dose of gentamicin. blood samples were taken and left for 1 hour to clot. Centrifuge blood sample for 10 twinkles at 5000 rpm to get a pure serum that was also stored at a 20-degree temperature. To estimate serum aspartate aminotransferase as well as alanine aminotransferase kit (Randox Laboratories Ltd. UK, recommending, colorimetric accouterments) were used.

Liver tissue washed with ice-cold saline and stored at 80-degree temperature. exercising cold potassium phosphate buffer, the liver was homogenized. Homogenates were separated at 5000 rpm for 10 twinkles at 4 ! and the supernatant was used for determining malondialdehyde and minimizing glutathione degree and exertion of catalase exercising colorimetric accouterments of the assay as framed by the manufacturer's instructions forbio-diagnostic (Bodaghi- Namilehet. al. 2018). Depending on the manufacturer, Cayman Chemical Co, USA, instructions, the degree

of nitric oxide (NO) level was determined by exercising a tackle of the colorimetric assay.

Statistical analysis

To assay the collected data, all the data were expressed as mean \pm S.E.M (pars of the repeated trials). A one-way analysis of friction (ANOVA) was done, followed by the Tukey test for the multiple comparisons. SPSS interpretation 21 was used. The differences were determined at the significance position of $p < 0.05$.

RESULTS

Effects of aspirin on the measured biochemical parameters

Treatment rats with gentamicin significantly increased liver weight compared to control rats (figure 1) whereas treatment rats with aspirin were suitable to reverse the effect of gentamicin on liver weight. While in Figure 2, dramatic increase in serum alanine aminotransferase and aspartate aminotransferase situations was witnessed in the animals that were subjected to gentamicin compared to the control group. Our results demonstrated that the treatment of aspirin, after gentamicin administration urged a significant reduction in the serum situations of the aminotransferases. Further, the treatment

with aspirin significantly suppressed hepatic lipid peroxidation and averted reductions in GSH position and catalase exertion because of gentamicin administration.

DISCUSSION

The current study aimed to examine the effect of aspirin against gentamicin-induced hepatotoxicity in a rat model. The results demonstrated that pre-treatment with aspirin significantly mitigated the adverse effects of gentamicin on liver weight, serum liver enzymes, and oxidative stress markers.

Gentamicin administration resulted in a dramatically elevation in liver weight, which is indicative of liver damage. This elevated liver weight may be caused by edema, congestion, and cellular infiltration caused by the toxic effects of gentamicin on hepatocytes⁸. However, pre-treatment with aspirin reversed this effect, suggesting a protective role against gentamicin-induced hepatotoxicity⁹⁻¹¹. The ability of aspirin to counteract the increase in liver weight may be attributed to its anti-inflammatory properties, as inflammation is known to contribute to liver injury. Aspirin's anti-inflammatory effects have been well documented and may involve the inhibition of pro-

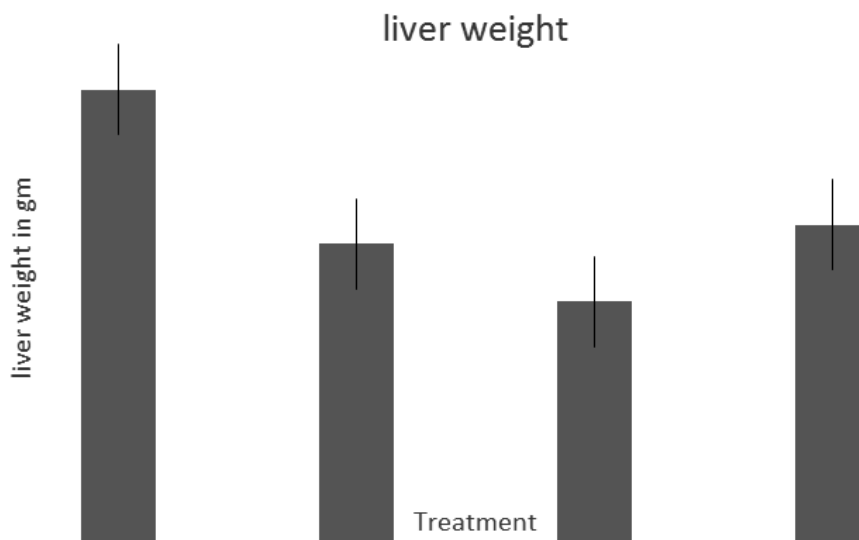


Fig. 1. Effect of aspirin on liver weight variation of gentamicin-induced hepatotoxicity in rats. N = 8; values expressed as mean \pm SEM * $P < 0.05$ Vs gentamicin Student's 't' test is used in data analysis

inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), and the modulation of various signaling pathways involved in the inflammatory response¹².

Elevation in liver enzymes is usually known as the prediction of hepatocellular damage. In this study, gentamicin administration led to a significant elevation in serum ALT and AST levels, indicating liver injury¹³. However, pre-treatment with aspirin significantly reduced the serum levels of these liver enzymes. This finding suggests that aspirin exerted a protective effect on liver cells and preserved their structural and functional integrity¹⁴⁻¹⁶. The mechanisms underlying the hepatoprotective effects of aspirin may involve the inhibition of inflammation-induced hepatocyte apoptosis and the modulation of oxidative stress pathways¹⁷. Aspirin has been shown to inhibit the release of pro-inflammatory mediators and to

promote the expression of anti-apoptotic proteins, thereby preventing hepatocyte damage and promoting cell survival.

Oxidative stress plays a crucial role in gentamicin-induced hepatotoxicity. Increased release of reactive oxygen species (ROS) and impaired antioxidant defense mechanisms contribute to liver cell damage¹⁸. In the present study, aspirin treatment significantly suppressed hepatic lipid peroxidation, as evidenced by the reduction in malondialdehyde (MDA) levels¹⁶. This indicates that aspirin acted as an antioxidant and attenuated lipid peroxidation, thereby protecting liver cells from oxidative damage. Aspirin's antioxidant properties may be attributed to its capability to kick free radicals out of the body, inhibit ROS production, and enhance the activity of endogenous antioxidant enzymes¹⁸⁻²².

Table 1. Effect of aspirin on antioxidant levels in gentamicin-induced hepatotoxicity in animals. All the values are expressed as mean \pm S.E.M., n = 8 in each group. ^a p < 0.05 vs. control group. ^b p < 0.05 vs. gentamicin

GSH (mg/g tissue)	NO (nmol/100mg tissue)	MDA	CATALASE (u/g tissue)	Dose (mg/kg)	Treatment
115.3 \pm 1.2	90.3 \pm 0.6	25.50 \pm 0.36	5.5 \pm 0.47		Control
105 \pm 4.3 ^a	102.3 \pm 1.55 ^a	51.71 \pm 1.03 ^a	3.4 \pm 0.32 ^a	100mg/kg	gentamicin
134.4 \pm 3.3	132.7 \pm 1.3	36.8 \pm 0.47	4.7 \pm 0.56	200mg/kg	aspirin
116.4 \pm 1.8 ^b	109.7 \pm 1.02 ^b	40.26 \pm 0.82 ^b	5.3 \pm 0.54 ^b		Aspirin+gentamicin

*MDA: malondialdehyde, NO: nitric oxide, GSH: glutathione.

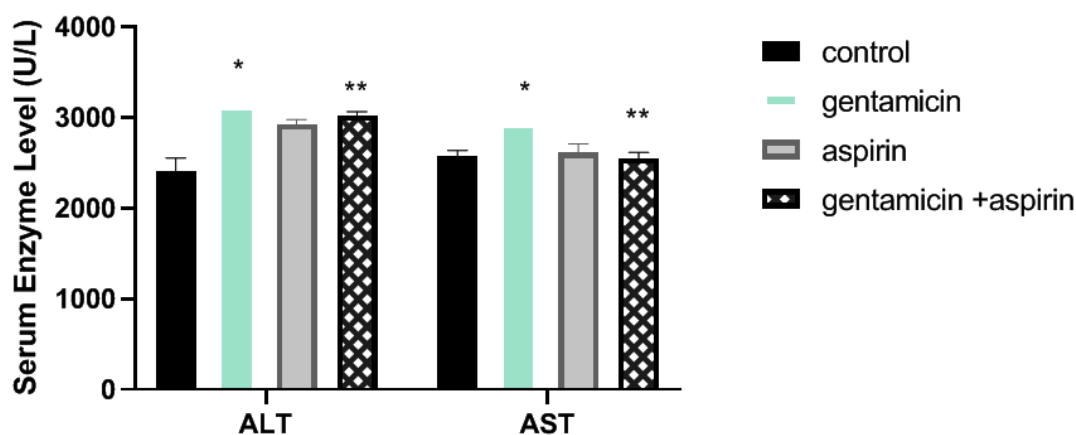


Fig. 2. Effect of aspirin on liver enzymes in rats with gentamicin-triggered hepatotoxicity. All the values are expressed as mean \pm S.E.M. (n = 8); *p < 0.05 vs. control group***p < 0.05 vs. gentamicin group).

Moreover, aspirin treatment reduced the depletion of glutathione (GSH) levels and catalase activity induced by gentamicin application. GSH is an important endogenous antioxidant that helps neutralize ROS and maintain redox balance in cells¹⁴⁻¹⁹. Catalase is an enzyme involved in the detoxification of hydrogen peroxide, a reactive oxygen species. The preservation of GSH levels and catalase activity by aspirin suggests its ability to enhance the antioxidant defense mechanisms in the liver and protect against oxidative stress-induced liver injury¹⁴⁻²⁰. Aspirin may exert its effects on GSH and catalase through the modulation of transcription factors and signaling pathways involved in antioxidant gene expression and activity.

The mechanism underlying the protective effect of aspirin against gentamicin-induced hepatotoxicity is likely multifactorial. Aspirin possesses anti-inflammatory properties, which can attenuate inflammation-induced liver injury. It also acts as an antioxidant, reducing oxidative stress and preventing oxidative damage to liver cells. Additionally, aspirin may modulate signaling pathways involved in cell survival and apoptosis, contributing to its hepatoprotective effects.

The findings of this study support previous research indicating the potential hepatoprotective properties of aspirin. However, further investigations are warranted to elucidate the exact molecular mechanisms underlying its protective effects and to determine the optimal dosage and duration of aspirin treatment for maximum efficacy. Additionally, future studies should explore the long-term effects of aspirin treatment, as well as its potential interactions with other medications commonly co-administered with gentamicin¹⁵.

CONCLUSION

In conclusion, this study demonstrates that pre-treatment with aspirin attenuates gentamicin-induced hepatotoxicity in a rat model. Aspirin mitigated liver damage, preserved liver function, and enhanced antioxidant defense mechanisms. These findings highlight the potential of aspirin as a protective agent against drug-induced liver injury. Further studies are needed to fully understand the mechanisms involved and to explore

its clinical applications in humans. The use of animal models provides valuable insights into the potential benefits of aspirin in the prevention and management of hepatotoxicity, but further clinical trials are necessary, especially in high-risk patients treated with gentamicin to establish its efficacy and safety in human patients¹³.

To conclude, the findings of this work provide evidence for the protective effect of aspirin against gentamicin-induced hepatotoxicity in a rat model. Pre-treatment with aspirin demonstrated beneficial effects on liver weight, serum liver enzymes, and oxidative stress markers. These findings suggest that aspirin possesses hepatoprotective properties and may be a potential therapeutic option for the prevention and management of drug-induced liver injury.

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Conflict of interest

The authors declare no conflict of interest.

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