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Gentamicin-Induced Hepatic Injury and Attenuating Role of Berberine

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Abstract

Globally, the incidence of hepatotoxicity is on the rise, which is a major public health concern. Despite the fact that gentamicin (GN) is considered a broad-spectrum antibiotic, excessive doses may have harmful effects on the body. Therefore, in this study, the hepatotoxicity induced by GN and the ameliorative effect of berberine (BR) were assessed in laboratory animals. In a laboratory experiment, a total of (32) rats were divided into four groups (N = 8): CR (control), GN (rats administered gentamicin at 80 mg/kg intraperitoneally), GN+BR (rats fed berberine 40 mg/kg orally 2 hours prior to gentamicin dose), and BR (rats provided only with berberine). All experimental groups continued their treatments for two weeks, and then rats were dissected to obtain the necessary samples for the examinations. Exposure to gentamicin resulted in liver dysfunction, as measured by significantly elevated serological levels of hepatic enzymes, and oxidative damage, as measured by augmentation in MDA and lowering in the activities of SOD and GSH in liver homologues. However, co-administration of berberine reversed significantly the serological levels of hepatic enzymes in the GN + BR group. In addition, the decreased concentration of MDA in liver tissues significantly restored the levels of SOD and GSH. It was determined that berberine can reduce gentamicin's hepatotoxicity.

Keywords

Gentamicin, Liver Dysfunction, Oxidative Stress, Laboratory Experiment.

One of the distinct metabolic activities of the liver is purification of deleterious substances from the body such as toxins and drugs [1,2] , and drug-induced liver injury is one of the critical reasons that limit the clinical interest of medications [3]. Injury may result in liver dysfunction such that it cannot perform activities properly and thus toxins can accumulate in the hepatic tissue [4,5]. It has been proven that some medical drugs can cause disruption in the mitochondrial function of liver cells, resulting in necrosis and hepatitis [6]. Hepatotoxicity can be considered as one of the most important toxic effects, as persistence of inflammation leads to cirrhosis and ends with liver failure [7]. Gentamicin (GN) is an aminoglycoside antibiotic commonly used to treat bacterial infections, and it is considered the drug of choice for many clinical cases because it has broad spectrum activity [8]. In contrast, use of GN in slightly higher doses has significant toxicity such as induction of nephrotoxicity as well as cochlear toxicity [9]. Besides, it may cause liver injury due to kidney damage [10]. It is known that pathological processes such as cytotoxicity are caused by oxidative stress, and experimental research has confirmed the ability of gentamicin to release reactive oxygen species, thus accelerating the process of lipid peroxidation [11-13]. Over time, interest in natural products as an alternative source for medicines is growing strongly, as they have a celebrity for their

effectiveness with minimal side effects. In addition, protective effects against drugs and chemicals toxicity in vitro as well as in vivo studies have been demonstrated after supplementation of medicinal plants or even their constituents. [14,15]. Berberine (BR), a benzyl tetra-isoquinoline alkaloid isolated from *Berberis* plants, belongs to the *Berberidaceae* family [16]. It has applicative since ancient times in traditional medicine, as it contains many pharmaceutical characteristics that have attracted the attentiveness of researchers. Several reports have highlighted the properties of BR in terms of antihypertensive, antiarrhythmic, anti-carcinogenic, anti-inflammatory, antibacterial, and anti-diabetic properties [17]. Besides, berberine has demonstrated a hepatoprotective effect against some toxins in laboratory animals in previous extensive studies [18], so aim of current study is to esteem the mitigating role of berberine upon liver injury induced by gentamicin in a rat model.

Methods and materials

Drug and herb extract

Gentamicin ampoules for Injection USP (80 mg /ml), obtained from Ryvis Pharma Company, Ontario, Canada. This anti-infective aminoglycoside used in current research to induce acute hepatotoxicity. Whereas, the Pure Naturals Berberine (500 mg) supplement was purchased from Pure Naturals™ Co., Jersey, USA. Berberine was prepared by dissolving the capsules in distilled water to facilitate the dosing of experimental rats.

Rats and experimental design

Total of 32 albino male rats, which weighing 170-195 g, were consumed. They were obtained from the animal houses of the scientific colleges of Iraqi Universities. These rats were placed in separate cages prepared for them with the availability of ideal environmental conditions in terms of temperature, moisture, lighting, ease of access to food and water. Besides, they were adapted for a week before the experiment. The rats were divided randomly into 4 groups, in each one (N= 8), and received treatment as explained in Table (1).

Table 1: Experiment protocol according to treatments and doses of the study groups

Groups	Dosage of treatments for (14) continued days
CR	Control rats were received distilled water (1mL) intraperitoneally (i.p).
GN	The animals were injected (i.p) with gentamicin (80 mg/kg/) [19].
GN +BR	Rats were provided with berberine (40 mg/kg) dissolved in (1mL) distilled water by gavage tube [20] two hours before gentamicin dosing.
BR	Rats were dosed with berberine (40 mg/kg) dissolved in (1mL) distilled water by gavage tube.

For 14 consecutive days the treatments were continued, and one day after the last dose, blood was collected from the hearts of the animals for serum separation. The anesthetized rats were autopsied, livers separated, and kept until used to assess the level of hepatic oxidative stress biomarkers.

Serum analysis

Sera required for the experiment were separated by centrifuging the blood at (7000) rpm for 15 minutes. Measurements of hepatic function biomarkers including aspartate aminotransferase (AST) as well as alanine aminotransferase (ALT) were performed using UV-visible spectrophotometer with manufacturer-customized reagent kits. Total bilirubin (TB) was also evaluated based on a previously described procedure [21].

Estimation of oxidative stress

Specific weights of liver tissue homogenates were prepared using special solutions, and supernatant of the homogenates was used for the determination of malondialdehyde (MDA), glutathione reductase (GSH) and superoxide dismutase (SOD), as previously described [22].

Data analysis

All analyzes were carried out using GraphPad Prism (9.0), and data were presented as mean and standard deviation. To determine variation within studied groups, a one-way analysis of variance (ANOVA) was applied, followed by Duncan's post hoc test. A p value < 0.05 was set as statistically significant.

Results

Gentamicin doses clearly impaired liver function through a significant elevation of serum AST (221.68±17.95) and ALT (183.82±7.15) activities. However, co-administration with berberine clearly reduced the detrimental effects of gentamicin on liver function, and thus significantly modified these higher values (124.18±14.62 and 121.86±5.45, respectively). In addition, a considerable increase in total bilirubin concentration was observed in gentamicin-intoxicated group (5.06±0.89). In contrast, co-treatment with BR reduced this high bilirubin level (13.26± 0.70), as illustrate in Figure (1).

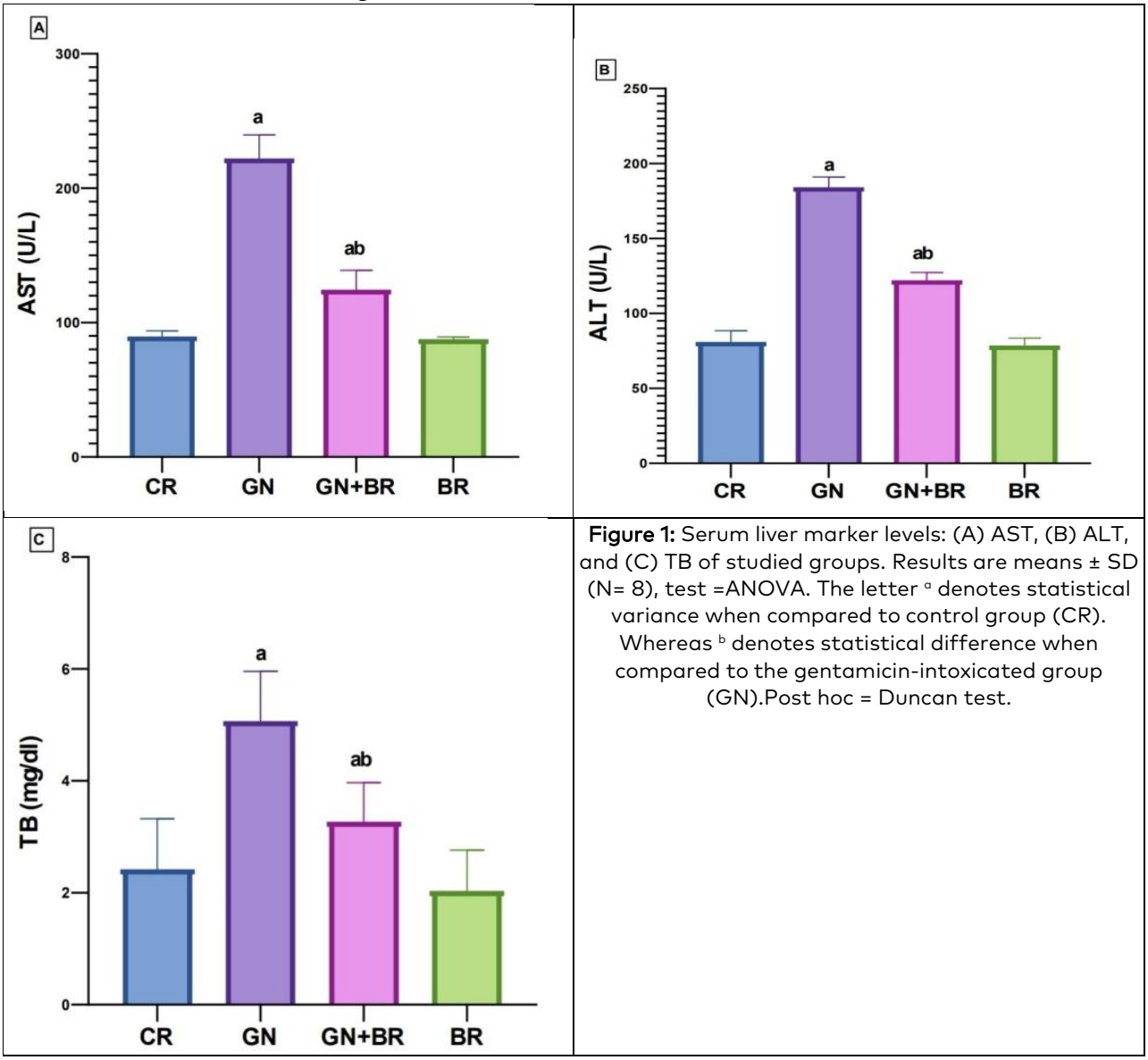

Figure 1: Serum liver marker levels: (A) AST, (B) ALT, and (C) TB of studied groups. Results are means ± SD (N= 8), test =ANOVA. The letter [a] denotes statistical variance when compared to control group (CR). Whereas [b] denotes statistical difference when compared to the gentamicin-intoxicated group (GN).Post hoc = Duncan test.

On the other hand, the results proved a clear increase in liver lipid peroxidation, thus indicating a high oxidative stress in the gentamicin-treated group (62.43±3.87). This was accompanied by an obvious decrease in both antioxidants' activities GSH (32.60±2.61) and SOD (33.47±2.98). Co-treatment of gentamicin with berberine resulted in a significant decrease in lipid peroxidation activity (41.89±2.58) conversely significantly increased glutathione reductase (41.28±3.47) and superoxide dismutase (45.73±2.11) activities, as shown in Figure (2).

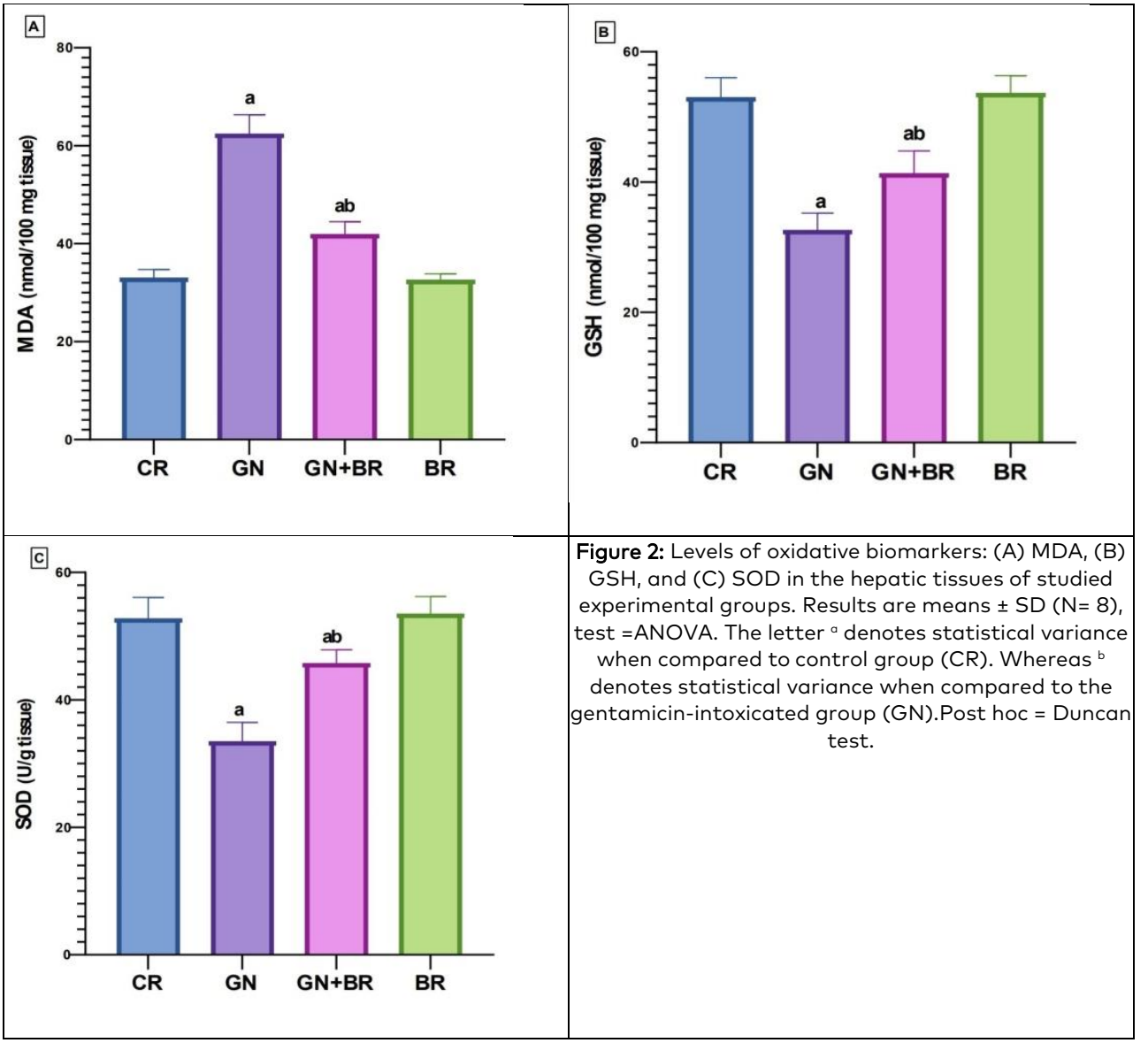

Figure 2: Levels of oxidative biomarkers: (A) MDA, (B) GSH, and (C) SOD in the hepatic tissues of studied experimental groups. Results are means ± SD (N= 8), test =ANOVA. The letter [a] denotes statistical variance when compared to control group (CR). Whereas [b] denotes statistical variance when compared to the gentamicin-intoxicated group (GN).Post hoc = Duncan test.

Discussion

It is well known that the liver has a major role in regulating many physiological processes, in addition to detoxifying many xenobiotics, besides detoxifying many xenobiotic drugs [23]. Although gentamicin (GN) is a common aminoglycoside antibiotic, potential nephrotoxicity and cytotoxicity are the main limitations for its clinical use [24]. On the other hand, several experimental studies have reported that gentamicin may cause hepatotoxicity by increasing the production of free radicals that lead to the creation of oxidative stress in hepatocytes [25-27].Thus, the destruction of hepatocytes by directing lipid peroxidation and other oxidative damage, and the enhancement of lipid peroxidation during microsomal ethanol metabolism in the liver leads to hepatitis and cirrhosis [23]. In this study, hepatic damage caused by GN administration was evidenced by a significant elevation in serum levels of ALT, AST, and TB when compared to a control subject. These results are in agreement with the founding of other similar studies [25-28]. In the context of clinical pathogenesis, increased serum aminotransferase (ALT and AST) concentrations as well as total bilirubin are indicators of liver dysfunction due to hepatocyte damage and liver injury [28–30]. This implies that oxidative stress has a main role in hepatic structural and functional impairment by alteration biochemical markers. In general, bilirubin is a breakdown product of erythrocytes secreted by the liver into the bile fluid. Therefore, if the bilirubin level is higher than normal,

this is a sign that the bilirubin is being excreted incorrectly, which means that the liver is not functioning properly [31]. In gentamicin-exposed rats, the results revealed notably decreased SOD and GSH activities in hepatic tissue homogenates with significantly increased MDA when compared with control animals. Other previous studies supporting our findings were conducted by Jafaripour *et al* [6], Khaksari *et al* [32] and Aziz *et al* [33]. Based on our findings, gentamicin induced overproduction of reactive oxygen species (ROS) and caused hepatotoxicity by altering the redox balance and antioxidants and disrupting membrane lipogenesis via lipid peroxidation thus increasing MDA [34]. This exponential increase in lipid oxidation by GN deteriorates membrane lipids causing hepatocyte necrosis and damage. Besides, the inhibited susceptibility of GN to antioxidants increases the production of ROS that detrimentally affect membrane lipids as well as degrade proteins and nucleic acids and thus hepatotoxicity and damage [28].The attrition of GSH activity may be due to over generation of free radicals or augment consuming of protecting SH group containing proteins. As for the decrease in the antioxidant SOD enzyme level, it has been related to the excess of superoxide anions and hydrogen peroxide production in the liver tissues [6,35].According to our results, co -treatment with berberine restored MDA, GSH, and SOD levels in liver tissue by scavenging free radicals and/or increasing antioxidant properties. The decrease in the level of hepatic biochemical biomarkers provided support with regard to the hypothesis, which confirmed that berberine is effective in maintaining hepatocyte membrane integrity [36, 37].

Berberine (BR) is a powerful antioxidant that was able to lower high hepatic enzymes levels in GN-induced hepatotoxic rats. The ameliorating effect of BR on liver injury is explained by diverse pathways including reducing the activity of inflammatory cytokines, inhibiting oxidative stress, and by inducing autophagy of hepatocytes [38]. In this respect BR may interfere with the stimulation of the purinergic receptor P2X7, and suppress the interception of the NLRP3 inflammatory pathway [39]. Besides, it diminishes the phosphorylation status of JNK1 as well as the creation of pro-inflammatory cytokines thereby reducing hepatocytes inflammation [40]. In addition, BR attenuates hepatotoxicity and oxidative damage by quenching free radicals and inhibiting antioxidant loss [41]. In a previous *in vivo* study by Hasanein and collagenous reported that berberine (50 mg/kg) corrected all perturbations in elevated levels of hepatic functional enzymes as well as markers of oxidative stress caused by lead intoxication. Thus it was able to mitigate hepatocyte damage, by reducing necrosis and infiltration of inflammatory cells [42]. In a similar study by Gholampour *et al* concluded that co-management with berberine (10 mg/kg) significantly reversed hepatic biochemical indicators and malondialdehyde levels in rats exposed to ferrous sulfate, reinforced by histological observations [43]. Also, Eftekhari et al confirmed the hepatoprotective effect of BR with therapeutic potential against paraquat-induced liver damage [44]. In a study conducted by Adel and colleagues, they concluded that berberine exerted a protective effect against gentamicin-induced nephrotoxicity in rats by restoring altered levels of antioxidants, inflammation, apoptosis indicators and depleted mitochondrial enzymes as well as improved histopathological changes [20]. Recently in 2022, Ke and colleagues conducted a rat model study, they reported that BR (200 mg/kg/day) over a month reduced alcohol-related liver injury [45].

Conclusion

This study showed that berberine has the ability to mitigate hepatic harm caused by gentamicin, through its anti-oxidant characteristics. It may be a better treatment approach against drug-induced liver damage. However, more experimentation studies are required to analyze the accurate molecular mechanisms and search the biological advantages to clarify the hepatoprotective impact of berberine more precisely.

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