Received: 7 May 2020 | Revised: 28 August 2020 | Accepted: 21 September 2020

DOI: 10.1111/bcpt.13502

ORIGINAL ARTICLE

BCPT Basic & Clinical Pharmacology & Toxicology

Human umbilical cord blood serum attenuates gentamicin-induced liver toxicity by restoring peripheral oxidative damage and inflammation in rats

Naser Mirazi[1] | **Fatemeh Baharvand**[1] | **Reza Moghadasali**[2] | **Alireza Nourian**[3] | **Abdolkarim Hosseini**[4]

[1]Department of Biology, Faculty of Basic Sciences, Bu-Ali Sina University, Hamedan, Iran

[2]Department of Stem Cells and Developmental Biology, Cell Sciences Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran

[3]Department of Pathobiology, Faculty of Veterinary Science, Bu-Ali Sina University, Hamedan, Iran

[4]Department of Animal Sciences and Biotechnology, Faculty of Life Sciences and Biotechnology, Shahid Beheshti University, Tehran, Iran

Correspondence
Naser Mirazi, Department of Biology, Faculty of Basic Sciences, Bu-Ali Sina University, Hamedan, Iran.
Email: mirazi205@gmail.com

Abstract

Gentamicin (GM) is an aminoglycoside antibiotic that despite its antibacterial effects, its use is restricted due to numerous side effects. The umbilical cord serum contains various biomolecules that have protective impacts on the damaged tissues. The aim of this study was to gauge the protective effect of human umbilical cord blood serum (hUCBS) on GM-induced hepatotoxicity. In this experimental study, 28 male Wistar rats, weighing 220 ± 20 g, were randomly categorized into 4 groups including control, GM (100 mg/kg), hUCBS at doses of 1 and 2% along with GM (100 mg/kg) for 10 days, intraperitoneally. Twenty-four hours after the last injection, direct blood sampling was taken from the heart to obtain blood serum and liver enzymes, inflammatory cytokines and liver tissue were examined for histology. GM causes necrosis and inflammation in liver tissue. Liver enzyme and inflammatory cytokine levels were significantly increased in the GM group. Human umbilical cord blood serum significantly decreased liver enzyme and inflammatory cytokines levels in the experimental groups compared to the GM group. GM causes liver damage such as the inflammation and necrosis in liver tissue. Treating the animals with hUCBS reduced the toxic effects of GM in the liver.

KEYWORDS

gentamicin, hepatotoxicity, inflammation, rat, umbilical cord blood serum

1 | INTRODUCTION

Gentamicin (GM) is an aminoglycoside antibiotic. Despite its clinical effects, its application has been restricted due to adverse side effects. The application of this antibiotic is a prevalent cause of acute renal failure in about 10 to 20% of the consumers.[1] Apart from the renal effects, GM also has hepatic effects that induce apoptosis and increase the activity of the reactive oxygen species (ROS).[2] Acute hepatic deficiencies caused by medication are associated with the rapid loss of hepatic function as well as high mortality rate. Currently, for the advanced conditions of the disease, the only alternative is the liver transplantation which due to the shortage of donors and rejection problems presents itself as a huge challenge.[3] However, in recent years, cell therapies utilizing stem cells—due to their inherent ability to repair damaged tissues and organs—have shown remarkable progress in advancing the recovery of damage and disability of organs and tissues.[4]

Having said that, the use of stem cells and their administration to patients entail serious risks and side effects such

as uncontrolled growth of transplanted cells.[5] Alternative methods such as cell-free methods and cell culture growth can be a viable approach for the treatment of the liver diseases.[6] Prior studies have revealed that cells derived from umbilical cord blood help restore the organ function and prevent the disease progression.[7] These studies demonstrate that these therapeutic effects are based on trophic factors mediated through immune regulators secreted from these cells.[7,8] Studies of proteomics report of human umbilical cord blood serum (hUCBS) indicate that hUCBS contains a high level of growth factors, cytokines, and immune mediators that affect immune and stem cell proliferation and function.[9,10] In recent years, this approach, namely the use of hUCBS, has been the cynosure of attention for the treatment of brain injury.[11] In this study, we probed the protective effects of hUCBS on GM-induced hepatotoxicity in male Wistar rats.

2 | MATERIAL AND METHODS

2.1 | Animals and their maintenance

In this experimental study, 28 adult male Wistar rats weighing 220 ± 20 g were purchased from Hamadan University of Medical Sciences and transferred to the animal room of Bu-Ali Sina University. The rats were maintained at 22 ± 3°C and 50%-60% humidity with 12 hours light cycle and 12 hours dark cycle. The rats had free access to water and food. To acclimatize the animals with the new atmosphere, the experiments were performed two weeks after the rats were accommodated. All conducted experiments pertaining to animal rights and conservation in this study were in accordance with the standard ethical guidelines (European Communities Directive 2010/63/EU) and were approved by Local Ethics Committee at the Bu-Ali Sina University (permit number: IR.BASU.REC.1398.035). The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.[12]

2.2 | Preparation of the hUCBS

The hUCBS needed for this study was obtained from Royan Institute of Academic Center for Education, Culture and Research in Tehran, Iran. The procedure was as such that after obtaining consent from caesarean mothers who had been screened for the infectious diseases such as HIV, hepatitis B and C virus, the cord blood was taken from the neonates. After the placenta was delivered with the umbilical cord, the umbilical cord was inserted into a sterile falcon tube, and the human umbilical cord blood was pumped into the tube and transferred to the laboratory in a closed tube, along with ice. It was incubated for two hours at room temperature and centrifuged at 20°C for 20 minutes after being coagulated at 3000 g. Blood serum was separated from the upper part of the tube by a sampler and poured into sterile tubes. The resulted serums from different donors were mixed together to minimize batch differences. Finally, the serums were kept at a temperature of −20°C until use.

2.3 | Study groups design

Gentamicin was obtained from Alborz Darou Pharmaceuticals Company (Tehran, Iran) in the form of 80 mg/mL ampoules. Each rat was given 100 mg/kg body weight to induce hepatotoxicity.[13] The rats were randomly divided into 4 groups of 7: control, GM (100 mg/kg), hUCBS at doses of 1 and 2% with GM (100 mg/kg) for 10 days.[14] All injections were done intraperitoneally with insulin syringe. At least a one-hour interval between GM injection and hUCBS was observed. The rats were anaesthetized 24 h after the last injection by ether (Merck, Germany) and T-sectioned from the abdominal area. Blood samples from each animal were poured into the test tubes, and the names of each group were recorded. After one hour, the samples were centrifuged for 10 minutes by blood centrifugation at 3000 *g* and their serums were separated.

2.4 | Biochemical and inflammatory cytokine measurements

In order to measure the amount of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) the ELISA Kit (Pars Azmoon Kit) and ELISA reader device (BioteTek ELx808) were used.

In order to gauge the amount of superoxide dismutase (SOD) and malondialdehyde (MDA) levels, the ELISA Kit (ZellBio GmbH) and ELISA reader device (BioteTek ELx808) were used. The sensitivity, intra-assay CV and inter-assay CV of the kit for SOD were 1 U/mL, 5.8% and 7.2%, respectively. The sensitivity, intra-assay CV and inter-assay CV of the kit for MDA were 0.1 μmol/mL, 5.8%, and 7.6%, respectively, based on manufacturer's instruction.

For assessment of interleukin (IL)-1β and tumour necrosis factor (TNF)-α levels in serum, the ELISA Kit (Invitrogen ELISA Kit), and ELISA reader device (BioteTek ELx808) were used. The sensitivity, intra-assay CV and inter-assay CV of the kit for IL-1β were 4.0 pg/mL, 10% and 10%, respectively. The sensitivity, intra-assay CV and inter-assay CV of

the kit for TNF-α were < 4.0 pg/mL, 5.8%, and 8.3%, respectively, based on manufacturer's instruction.

2.5 | Histopathological staining

After the incision of the abdomen of each animal, the liver tissue was removed and washed with saline and transferred to a 10% formalin-containing container (having 10 times of the sample volume). In the next step, tissues were dehydrated and blocked for histological examination. From these tissues, 5μ-size sections were prepared and stained through the haematoxylin-eosin method.

2.6 | Statistical analyses

The data were expressed as mean ± standard deviation (SD). The data were analysed using GraphPad Prism version 8 software, and one-way ANOVA was used to determine the level of significance. If significant, then the Tukey test would be used. Significance level was set at 0.05 to interpret the results of the tests used. The elicited slides magnified at 400 were scrutinized for microscopic studies.

3 | RESULT

3.1 | Results of histopathological studies

Histopathological observations in tissue slides of the control group showed that different parts of the liver tissue included normal hepatocyte cells, with no signs of inflammation, necrosis and lymphocyte presence in the liver tissue (Figure 1A). The microscopic examination of liver tissue in the GM group revealed that GM resulted in necrosis in the hepatocyte cells, and extensive influx of inflammatory cells between the liver tissues (Figure 1B). Liver histology examination in experimental hUCBS 1% group showed that necrosis of hepatocyte cells and the infiltration of leukocytes into the interstitial space was observed, although relative to the GM group, tissue damage was seen to be less (Figure 1C). The histological examination of the liver in experimental hUCBS 2% group showed that tissue protection was implemented well against GM-induced damage, hepatocyte cell necrosis and inflammatory cell aggregation were not observed (Figure 1.D). The quantitative analysis of the histological morphometric study is shown in Table 1. The amount of hepatocyte cells in the GM-treated group unveiled a significant decrease compared to the control group ($P < .001$). Treatment with hUCBS

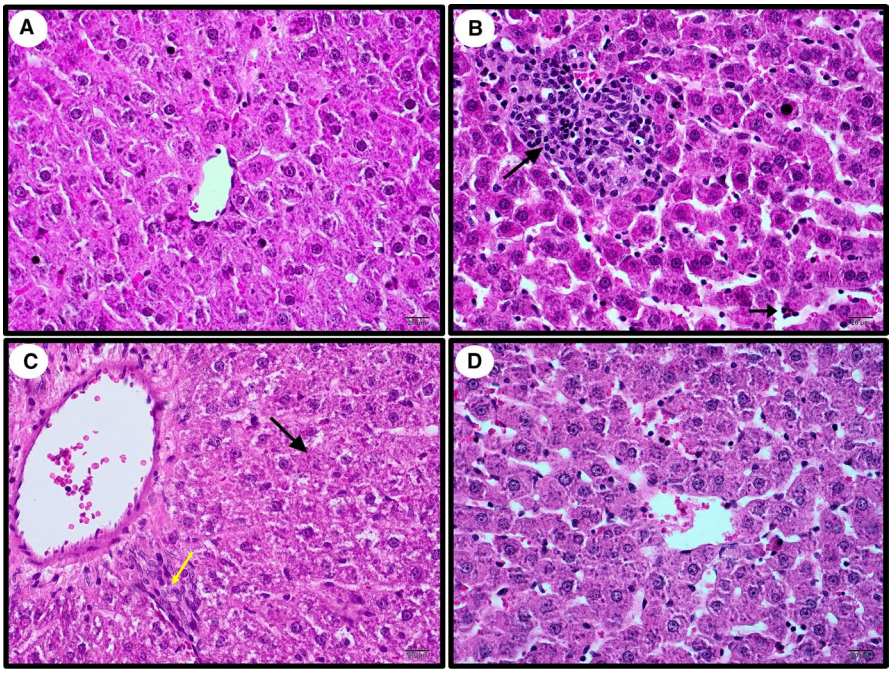

FIGURE 1 Micrographs of liver hepatocyte from the normal and treated rats. (A) hepatocyte cells with normal arrangement of tissue section of liver prepared in the control group. Hepatocytes are perfectly normal. The central lobular vein and its associated hepatocyte scaffolds are naturally seen; (B) Tissue section prepared from liver of GM-treated group. Lymphocyte influx (black arrow) is observed in the liver tissue. The cellular scaffold disintegrates, and necrosis is created in the hepatocytes; (C) Tissue section prepared from liver of hUCBS 1% group. Inflammation in the liver tissue has decreased, and the influx of lymphocytes has decreased (yellow arrow). Hepatocyte necrosis is still present (black arrow). The cellular scaffold is returning to normal state; (D) Tissue section prepared from the liver of hUCBS 2% group. The centeral lobular vein is almost normal, and the cellular scaffold is reaching normal state. The rate of necrosis has decreased. Lymphocytic infiltration is gone, and inflammation is reduced. Haematoxylin-eosin staining with 400 × magnification

TABLE 1 The number of hepatocytes in different treatment groups

Experimental groups	Number of hepatocytes
Control	108.70 ± 7.13
GM 100	86.40 ± 7.91[a]
GM 100 + hUCBS 1%	99.80 ± 9.62[b]
GM 100 + hUCBS 2%	102.10 ± 11.74[c]

Note: The protective effect of hUCBS on liver was quantitatively assessed by counting hepatocytes in 10 microphotographs for each group taken from random fields of the tissue sections (×400 magnification, 90,000 μm^2, H&E). Data are shown as mean ± SD.

[a]$P < 0.001$ *vs*. control.

[b]$P < 0.05$.

[c]$P < 0.01$ *vs*. GM 100 group.

1% and 2% compared with GM group showed a significant improvement in number of hepatocyte cells ($P < .05$ and $P < .01$, respectively).

3.2 | The effect of hUCBS on the liver enzymes

Table 1 shows the changes in the serum levels of the liver biochemical enzymes after treatments either with GM or hUCBS. One-way ANOVA showed significant difference [$F(3,24) = 30.69$, $P < .001$] in the amount of AST enzyme among the groups. The amount of AST enzyme in the GM-treated group revealed a significant increase compared to the control group ($P < .001$). Treatment with hUCBS (1 and 2%) showed a significant decrease compared to the GM group ($P < .01$ and $P < .001$, respectively).

One-way ANOVA showed significant difference [$F(3,24) = 28.28$, $P < .001$] in the amount of ALT enzyme among the groups. The amount of ALT in the GM-treated group unveiled a significant increase compared to the control group ($P < .001$). This enzyme in the experimental hUCBS 1% group compared with GM group showed a significant decline ($P < .05$). This decrease was more significant in the experimental hUCBS 2% group compared to the GM group ($P < .001$).

One-way ANOVA showed significant difference [$F(3,24) = 28.48$, $P < .001$] in the amount of ALP enzyme among the groups. The level of ALP enzyme in the GM-treated group demonstrated a significant increase ($P < .01$); the level of this enzyme in the experimental hUCBS 1% group was higher compared to the control group ($P < .05$). Higher doses of hUCBS (2%) demonstrated a significant decrease compared to the GM group ($P < .01$).

3.3 | The effect of hUCBS on the oxidative damage

One-way ANOVA showed significant difference [$F(3,24) = 6.38$, $P < .01$] in the amount of SOD enzyme among the groups. The evaluation of serum levels of SOD revealed that GM significantly decreased the enzyme levels in rats. Treatment with hUCBS 1% although did increase SOD, it did not show a significant difference with the control group and the GM group. This result for the group receiving a high dose of hUCBS 2% significantly increased SOD enzyme compared to the GM group ($P < .01$) (Figure 2A).

One-way ANOVA showed significant difference [$F(3,24) = 22.53$, $P < .001$] in the amount of MDA enzyme among the groups. The results of the study of serum levels of MDA in the tested rats indicated that the use of GM significantly augmented the serum level of MDA in rats. This was significantly reduced in the hUCBS (1 and 2%) treatment group compared to the GM group (Figure 2B).

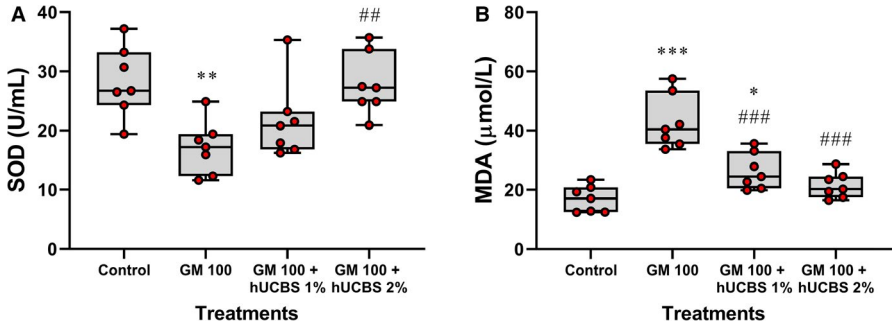

FIGURE 2 Comparing the serum level of SOD (A) and MDA (B) in the different experimental groups. Each box showing the minimum score, first quartile, median, third quartile, and maximum score is related to seven male Wistar rats. Signs are showing the significant meaningfulness in changing the levels of SOD and MDA after the treatments. *, $P < .05$; **, $P < .01$; ***, $P < .001$; *vs*. control; ##, $P < .01$; ###, $P < .001$; *vs*. GM 100 group

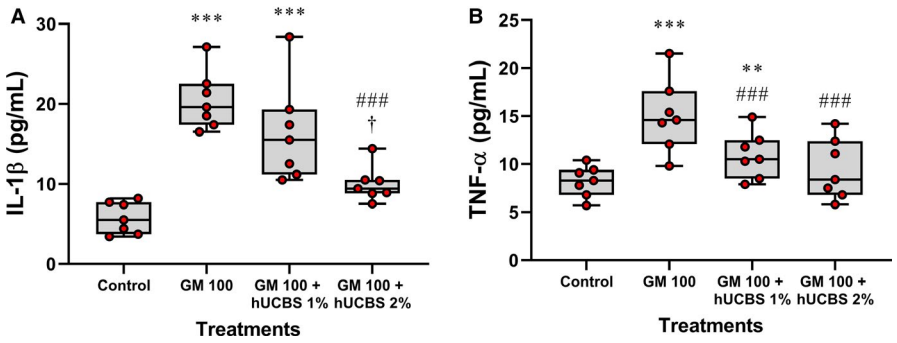

FIGURE 3 Comparing the serum level of IL-1β (A) and TNF-α (B) in the different experimental groups. Each box showing the minimum score, first quartile, median, third quartile, and maximum score is related to seven male Wistar rats. Signs are showing the significant meaningfulness in changing the levels of IL-1β and TNF-α after the treatments. **, $P < .01$; ***, $P < .001$; *vs*. control; ###, $P < .001$; *vs*. GM 100; †, $P < .05$; *vs*. GM 100 + hUCBS 1% group

3.4 | The effect of hUCBS on the inflammatory cytokines

Analysis by one-way ANOVA showed significant difference [$F(3,24) = 19.77$, $P < .001$] in the amount of IL-1β among the groups. Findings of the serum levels of IL-1β in the blood of the tested rats designated that GM significantly increased IL-1β levels in the group treated by this drug. On the other hand, the use of hUCBS 1% did not significantly decrease it, compared to the GM groups. However, the use of hUCBS 2% significantly decreased it in comparison with the GM group (Figure 3A).

ANOVA analysis showed significant difference [$F(3,24) = 7.61$, $P = .001$] in the amount of TNF-α among the groups. The results of serum levels of TNF-α in the assessed rats indicate that while the use of GM in the treatment of rats significantly increases the serum level of TNF-α in this group of rats, the use of hUCBS in the tested rats causes a significant decrease in the serum level of TNF-α in the blood of rats treated with hUCBS. The results also unveiled that the levels of TNF-α serum in the blood of rats receiving high dosages of hUCBS were also significantly decreased *vs*. the group receiving the low dosage of hUCBS (Figure 3B).

4 | DISCUSSION

This study was designed to investigate the protective effects of hUCBS on GM-induced hepatotoxicity in male rats. The results of this study signify that the injection of GM at a dose of 100 mg/kg body weight for 10 consecutive days caused hepatotoxicity in liver tissues of the rats. This abnormality in the tissues led to the elevation of AST, ALT and ALP liver enzymes. The findings of this study are in line with the results of previous studies.[15] These results also give credence to this observation that gentamicin has deleterious effects on liver tissue. Tissue studies also confirm that GM causes lymphocyte secretion and hepatocyte necrosis. Khaksari M et al, (2019) reported that GM can impair liver function and increase liver enzymes. The mechanism and the main cause of GM-induced hepatotoxicity are not known precisely; however, the induction of hepatocyte apoptosis by GM administration leads to such process.[16] Arjinajarn et al, (2017) stated that hepatic tissue inflammation and hepatocyte apoptosis are the most important side effects of GM consumption.[17] The mechanism of the effect of GM on the body's tissues is the creation of apoptosis or the planned cell death and free radical production. Free radicals can have umpteen

TABLE 2 Comparison of the serum ALT, AST and ALP level in the control, GM 100, hUCBS 1% and hUCBS 2% groups

Experimental groups	ALT (U/L)	AST (U/L)	ALP (U/L)
Control	62.14 ± 20.91	201.6 ± 26.68	97.71 ± 11.04
GM 100	169.3 ± 31.64[c]	408.0 ± 59.26[c]	205.1 ± 40.83[b]
GM 100 + hUCBS 1%	122.1 ± 15.85[b,d]	275.7 ± 22.07[b,e]	171.9 ± 26.68[a]
GM 100 + hUCBS 2%	82.43 ± 22.91[f]	201.3 ± 62.84[f]	104.7 ± 13.63[e]

Note: Data are shown as mean ± SD of seven animals per group.

[a]$P < 0.05$.

[b]$P < 0.01$.

[c]$P < 0.001$ *vs*. control.

[d]$P < 0.05$.

[e]$P < 0.01$.

[f]$P < 0.001$ *vs*. GM 100 group.

destructive effects on the organs such as the liver and kidney.[2] Gentamicin also has toxic effects on various tissues by causing oxidative reactions and cellular damage. The most important bio-damage of reactive oxygen metabolites is the reaction with unsaturated lipids resulting from their peroxidation. These effects alter the fluidity of the membrane and, as a result, the membrane is permeable to molecules even as large as enzymes.[18] Aminotransferases are representative of hepatocyte health. Alanine aminotransferase is basically found in the liver. Therefore, it is a better parameter for the diagnosis of liver injury, but AST also shows bile function and is found in other tissues.[19]

The findings of the present study demonstrate that for the protection against GM-induced hepatotoxicity, hUCBS accompanied by GM dose-dependently causes a reduction in the tissue damage and a decrease in the serum levels of hepatic enzymes as such that the treatment through it staves off the elevation of liver enzymes' level resulted from the GM toxicity. The tissue damage was also decreased in the serum-receiving group at higher doses than in the GM group. The histological examination of tissue sections prepared from the test specimens also confirms such results. There are reports of the effects of some drugs, including GM, which may have the side effect of altering the serum level of SOD. Superoxide is a secondary by-product of the oxygen metabolism and, in case it goes unregulated, brings about umpteen types of cellular damage.[20] Hydrogen peroxide, or oxygenated water, is also detrimental to the cell and is degraded by other enzymes such as catalases. Thus, superoxide dismutase is one of the principal types of the antioxidant defence system and is present in almost all cells exposed to oxygen. Arjinajarn et al, (2017) reported that GM reduces serum SOD levels.[17] This report is in line with the results of the present study. The results of this study showed GM-induced damage in rat liver which resulted in a significant decrease in SOD serum level. The use of hUCBS in the GM-treated groups displayed a significant increase in the serum level of SOD. The antioxidant compounds present in hUCBS are assumed to be responsible for this increase in SOD.

The chemicals or drugs that cause lipid peroxidation can also disrupt the functioning of tissues, including liver tissue. Such a disorder can cause increased levels of MDA in the blood serum and tissues. In 2020, Abdelrahman et al showed that GM induced oxidation of lipids in renal and hepatic tissues and increased serum levels of MDA.[21] In a recent study, GM also induced an increase in serum MDA. The concurrent administration of hUCBS and GM in the test groups significantly decreased serum MDA compared to the GM group. This influence may be due to the effects of chemical substances and compounds on protein macromolecules and some chemokines present in hUCBS that have healing and anti-apoptotic effects on tissues damaged by GM.

Gentamicin is an aminoglycoside that can cause inflammation and increase IL-1β in various tissues including kidney and liver.[22] The results also showed that gentamicin intake in rats was associated with increased IL-1β. The serum levels of IL-1β were significantly decreased in the groups using GM simultaneously with hUCBS. hUCBS has been reported to inhibit the synthesis of prostaglandins and interleukins.[23] These factors are likely to inhibit the process of interleukin formation in the liver and this is because the groups receiving hUCBS exhibited a significant decrease in IL-1β serum levels compared to the control group. There are several reports indicating an increased effect of TNF-α in the blood serum of GM-treated rats. Arjinajarn et al, in 2017 showed that gentamicin increased swelling, hepatocyte apoptosis and elevated serum TNF-α levels in rats.[17] Edeogu et al (2019) probed the seed oil effects of *Moringa oleifera* on the GM-induced nephrotoxicity and concluded that GM significantly increased the serum levels of TNF-α and IL-1β in rats.[24] Han et al (2020) also reported that GM significantly increased inflammatory factors such as TNF-α.[25] These reports are all consistent with the results of the present study. The presence of natural and pharmacological protective agents may decrease the elevation of TNF-α in the blood serum of the rats treated with them. The hUCBS levels of TNF-α are also reduced due to its many natural protective compounds.

5 | CONCLUSION

The results of this study signal that GM causes liver tissue damage as well as elevated liver enzyme levels. The hUCBS has protective effects on GM-induced liver damage, which may be pertained to the biomolecules present in hUCBS that are having strong anti-inflammatory and antioxidant properties.

ACKNOWLEDGEMENTS

The authors give special thanks to Dr Morteza Zarrabi at the Royan Stem Cell Technology and Cord Blood Bank (Tehran, Iran) for providing human umbilical cord blood serum for this research.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in this study.

ORCID

Naser Mirazi https://orcid.org/0000-0002-8664-3220

REFERENCES

1. Hayward RS, Harding J, Molloy R, et al. Adverse effects of a single dose of gentamicin in adults: a systematic review. *Br J Clin Pharmacol* 2018;84:223-238.

2. Stojiljkovic N, Stoiljkovic M, Randjelovic P, Veljkovic S, Mihailovic D. Cytoprotective effect of vitamin C against gentamicin-induced acute kidney injury in rats. *Exp Toxicol Pathol.* 2012;64:69-74.
3. Grek A, Arasi L. Acute liver failure. *AACN Adv Crit Care.* 2016;27:420-429.
4. Dai W, Hale SL, Martin BJ, et al. Allogeneic mesenchymal stem cell transplantation in postinfarcted rat myocardium: Short- and long-term effects. *Circulation* 2005;112:214-223.
5. Amariglio N, Hirshberg A, Scheithauer BW, et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. *PLoS Med* 2009;6(2):e1000029.
6. Yang C, Wang G, Ma F, et al. Repeated injections of human umbilical cord blood-derived mesenchymal stem cells significantly promotes functional recovery in rabbits with spinal cord injury of two noncontinuous segments. *Stem Cell Res Ther* 2018;9:136.
7. Park JH, Park J, Hwang SH, Han H, Ha H. Delayed treatment with human umbilical cord blood-derived stem cells attenuates diabetic renal injury. *Transplant Proc.* 2012;44:1123-1126.
8. Garbuzova-Davis S, Rodrigues MCO, Mirtyl S, et al. Multiple intravenous administrations of human umbilical cord blood cells benefit in a mouse model of ALS. *PLoS One* 2012;7(2):e31254.
9. Doorn J, Moll G, Le Blanc K, van Blitterswijk C, de Boer J. Therapeutic applications of mesenchymal stromal cells: paracrine effects and potential improvements. *Tissue Eng Part B Rev.* 2012;18:101-115.
10. Fan C-G, Zhang Q-J, Zhou J-R. Therapeutic potentials of mesenchymal stem cells derived from human umbilical cord. *Stem Cell Rev Rep.* 2011;7:195-207.
11. Yoo J, Kim H-S, Seo J-J, et al. Therapeutic effects of umbilical cord blood plasma in a rat model of acute ischemic stroke. *Oncotarget.* 2016;7:79131-79140.
12. Tveden-Nyborg P, Bergmann TK, Lykkesfeldt J. Basic & Clinical Pharmacology & Toxicology Policy for Experimental and Clinical studies. *Basic Clin Pharmacol Toxicol* 2018;123:233-235.
13. Ademiluyi AO, Oboh G, Owoloye TR, Agbebi OJ. Modulatory effects of dietary inclusion of garlic (*Allium sativum*) on gentamycin-induced hepatotoxicity and oxidative stress in rats. *Asian Pac J Trop Biomed.* 2013;3:470-475.
14. Caseiro AR, Ivanova G, Pedrosa SS, et al. Human umbilical cord blood plasma as an alternative to animal sera for mesenchymal stromal cells in vitro expansion - A multicomponent metabolomic analysis. *PLoS One* 2018;13(10):e0203936.
15. Rashid U, Khan MR. Fagonia olivieri prevented hepatorenal injuries induced with gentamicin in rat. *Biomed Pharmacother* 2017;88:469-479.
16. Khaksari M, Esmaili S, Abedloo R, Khastar H. Palmatine ameliorates nephrotoxicity and hepatotoxicity induced by gentamicin in rats. *Arch Physiol Biochem.* 2019;1-6. https://doi.org/ 10.1080/13813455.2019.1633354.
17. Arjinajarn P, Chueakula N, Pongchaidecha A, et al. Anthocyanin-rich Riceberry bran extract attenuates gentamicin-induced hepatotoxicity by reducing oxidative stress, inflammation and apoptosis in rats. *Biomed Pharmacother* 2017;92:412-420.
18. Bergamini CM, Gambetti S, Dondi A, Cervellati C. Oxygen, reactive oxygen species and tissue damage. *Curr Pharm Des* 2004;10:1611-1626.
19. Vozarova B, Stefan N, Lindsay RS, et al. High alanine aminotransferase is associated with decreased hepatic insulin sensitivity and predicts the development of type 2 diabetes. *Diabetes* 2002;51:1889-1895.
20. Hayyan M, Hashim MA, AlNashef IM. Superoxide Ion: Generation and Chemical Implications. *Chem Rev* 2016;116:3029-3085.
21. Abdelrahman RS, Abdelmageed ME. Renoprotective effect of celecoxib against gentamicin-induced nephrotoxicity through suppressing NFκB and caspase-3 signaling pathways in rats. *Chem Biol Interact* 2020;315:108863.
22. Öztopuz Ö, Türkön H, Sehitoglu MH, et al. Hyperbaric oxygen treatment ameliorates gentamicin-induced nephrotoxicity and expression of kidney injury molecule 1 in the rat model. *Undersea Hyperb Med.* 2019;46:125-133.
23. Chen C-T, Foo N-H, Liu W-S, Chen S-H. Infusion of human umbilical cord blood cells ameliorates hind limb dysfunction in experimental spinal cord injury through anti-inflammatory, vasculogenic and neurotrophic mechanisms. *Pediatr Neonatol.* 2008;49:77-83.
24. Edeogu CO, Kalu ME, Famurewa AC, Asogwa NT, Onyeji GN, Ikpemo KO. Nephroprotective effect of *Moringa oleifera* seed oil on gentamicin-induced nephrotoxicity in rats: biochemical evaluation of antioxidant, anti-inflammatory, and antiapoptotic pathways. *J Am Coll Nutr.* 2019;39(4):307-315.
25. Han C, Sun T, Liu Y, Fan G, Zhang W, Liu C. Protective effect of Polygonatum sibiricum polysaccharides on gentamicin-induced acute kidney injury in rats via inhibiting p38 MAPK/ATF2 pathway. *Int J Biol Macromol.* 2020;151:595-601.

How to cite this article: Mirazi N, Baharvand F, Moghadasali R, Nourian A, Hosseini A. Human umbilical cord blood serum attenuates gentamicin-induced liver toxicity by restoring peripheral oxidative damage and inflammation in rats. *Basic Clin Pharmacol Toxicol*. 2020;00:1–7. https://doi.org/10.1111/bcpt.13502