OPEN ACCESS

Haya: The Saudi Journal of Life Sciences

Abbreviated Key Title: Haya Saudi J Life Sci
ISSN 2415-623X (Print) | ISSN 2415-6221 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

Functional Assessment of MGO Nanoparticle Supplementation in an Acute Liver Injury Rat Model

Muhammad Tamoor Mansha[1], Ayesha Maqbool[2], Nabeela Nadir[3*], Ali Imran Mallhi[4], Sehar Arshad[1], Maira Munir[5], Fahad Ali Nadeem[6], Mubashir Ahmad[7], Aftab Hussain[8]

[1]Department of Physiology, Government College University Faisalabad, Kotwali Rd, Gurunanakpura, Faisalabad, Punjab 38000, Pakistan
[2]Department of Zoology, Wildlife and Fisheries, University of Agriculture, Faisalabad, Pakistan
[3]Department of Zoology, University of Education Lahore, Faisalabad Campus, Pakistan
[4]Department of Applied Chemistry, Government College University Faisalabad, Kotwali Rd, Gurunanakpura, Faisalabad, Punjab 38000, Pakistan
[5]Department of Zoology, Lahore College for Women University, Lahore, Pakistan
[6]Faculty of Science & Technology, University of Central Punjab, Avenue 1, Khayaban-e-Jinnah، Road, Johar Town, Lahore, Punjab, Pakistan
[7]Institute of Zoology, University of the Punjab, F7H8+HFV, Canal Rd, Quaid-i-Azam Campus, Lahore, Punjab, Pakistan
[8]Department of Animal Sciences, University of Veterinary and Animal Sciences Lahore, Sub-Campus Jhang

DOI: 10.36348/sjls.2023.v08i11.001 | **Received:** 16.10.2023 | **Accepted:** 20.11.2023 | **Published:** 02.12.2023

***Corresponding author:** Nabeela Nadir
Department of Zoology, University of Education Lahore, Faisalabad Campus, Pakistan

Abstract

Magnesium supplements have been effective for modulating process of bile resistance, decrease oxidative stress and systemic inflammation. Current study was designed to functionally evaluate the MgO nanoparticle supplementation in an acute liver injury rat model. The animals were randomly divided into five groups. All groups were administrated with CCl4 to induce hepatic injury except of negative control group which received only vehicle. CCl4 administration is followed by MgO nanoparticles in the concentration of 150 and 300 mg/kg in low dose and high dose treated group respectively except of standard control group. After 21 days of treatment, the animals were sacrificed to collect blood and liver samples. Serum levels of bilirubin, AST, ALT and ALP were determined. Liver sample was also subjected to RNA isolation by Trizol method followed by the cDNA synthesis and Real Time PCR. In addition, lipid profile was also assessed. The data obtained was analyzed by one way analysis of variance (ANOVA). The results showed that levels of bilirubin, AST, ALT and ALP were significantly elevated in positive control group while MgO treated groups, somehow, had normal ranges of these enzymes. Furthermore, the qPCR results showed that the expression of Farnesoid X receptor (FXR), transcriptional regulator of the bile salt export pump (BSEP) and sodium taurocholate cotransporting polypeptide (NTCP), is reduced in positive control group, while nanoparticles treated groups had normal expression of these genes. In conclusion, our data showed that MgO nanoparticles possess hepatoprotective activity against hepatic injury.

Keywords: MgO nanoparticles, qPCR, sodium taurocholate, polypeptide, biological activity.

INTRODUCTION

Nanomaterial always employed in cosmetics, food goods, antimicrobial products, and therapeutic preparations in biomedical applications. Nanoparticles (NPs) show better dispensability, colloidal stability in biological environments, high internalization efficiency, and lower toxicity than equivalent micro particles (MPs). The higher cell permeability and greater quantum effects as a function of NP size are due to their unique physicochemical features (Ivask *et al.*, 2015). Histopathological study is required to establish the morphological alterations caused by NPs exposure, as well as to evaluate the toxicological effects on the liver, kidney, heart, spleen, and brain. When compared to MPs, NPs have differing rates of absorption, persistence, dispersion, accumulation, and elimination, resulting in a powerful interaction with animal models (Dumala *et al.*, 2017).

Mg shortage has been linked to muscular dystrophy, which leads to elevated SGOT and SGPT activity in the blood. As a result, Mg has an indirect link with the activities of serum SGOT and SGPT. Sekine *et al.*, (1988) found that serum SGOT activity in steers was low in the early fattening stage but grew to 80 units by the mid-fattening stage and through the fattening duration. Young calves showed lower SGOT and SGPT activity than mature cows (Cornelius *et al*., 2001).

The effects of Mg supplementation and housing type on serum SGOT and SGPT activities in beef cows have received little attention. Cattle do not control their mineral intake according to their demands, according to (Standish, 2010).

The effects of 10- and 50-nm GNPs on the production of the proinflammatory cytokines IL-1, IL-6, and TNF- in the liver of rats were examined in this study. Magnesium (Mg) is an important intracellular cation and mineral in the human body's living cells. The association between Mg shortage and T2D is well-known. The most major processes contributing to Mg depletion in persons with T2D are a low Mg intake and excessive urine excretion. Tyrosine kinase activity is affected by magnesium shortage, which leads to insulin resistance; however, replenishment increases enzyme activity (Barbagallo, 2015).

Human exposure to nanoparticles, particularly metal-based nanoparticles, has increased drastically as a result of their presence as a pollutant in water, air, and food products as a result of natural occurrences or increased anthropogenic activities. MgO nanoparticles, as one of the metal-based nanoparticles, are widely employed as a catalyzer, redactor, humidity sensor, antibacterial agent, and destructive sorbent for poisons, fluoride, and other contaminants, as well as in enhancing UV emission luminous efficiency. MgO-based magnetic tunnel junction sensors, in combination with magnetic nanoparticles, have recently been used as biosensors for liver cancer immunoassay, and MgO nanoparticles have been identified as a promising material for tumor therapy using Nano-cryosurgery (Hess *et al*., 2010).

Chronic liver disease is a critical global health issue that causes a significant economic and social cost around the world. Alcohol misuse, viral hepatitis infections, fatty liver, autoimmune, genetic, and metabolic illnesses, harmful effects of some medicines or intoxication with specific chemicals are all causes of liver disease. Early intervention may be able to slow the progression of liver disease and even reverse it. Hepatic fibrosis, cirrhosis, and cancer develop as a result of ineffective treatment. The progression of chronic liver disease to end stage is associated with a significant rate of morbidity and mortality (Madrigal-Santillán *et al*., 2014).

Oxidative stress is one of the main causes of liver damage. Drugs' hepatoprotective effects are thought to be mostly due to antioxidant qualities that activate the body's natural antioxidant defense mechanism. Other pharmacological mechanisms, however, appear to have a role in hepatoprotective effects, according to emerging research. Despite contemporary medicine's enormous improvements, there is currently no fully effective treatment that can provide complete liver protection. Due to limited therapeutic effects or severe consequences, this is the case. As a result, there is an increasing need to take up unique and unconventional ways (Akbartabar, 2015).

Zein-coated magnesium oxide nanowires could be used as an efficacious antimicrobial material which could be used for the formulation of variety of dental products. Anyhow, information about the toxic effects on human health is still unclear. A 21-day continual medication was preceded. We divided wistar rats into two groups, such as, males and females (n = 18) and each group was further subdivided into 3 subgroups: control group, MgO-zein nanowires low dose group, MgO-zein nanowires high dose group. The low dose used was 100 mg/kg while the high dose used was 200 mg/kg. The results depicted that Magnesium oxide zinc coated nanowires did not influence the levels of electrolytes at both doses as compared to the control group. Additionally, these nanowires did not make any obvious change in hepatic markers in both genders of rats. MgO-zein nanowires at both dosages did not depict any impelling change in serum creatinine in treated rats of both genders. However, little histological changes were determined in both doses of Magnesium oxide-zein coated nanowires in kidney and liver of both genders. Magnesium oxide nanoparticles are used worldwide in many therapeutic fields. Zein served as in medicine applications particularly applying the tablet over sugar (Naguib *et al.*, 2021).

MATERIAL AND METHODS

Animal Model

In this study, albino rat weighing 150-300g were used. Mice were raised for almost 8 weeks in the animal house of Physiology GCUF to make them familiarize with the environment. The standard laboratory conditions with regulated temperature were sustained during the experimental period of 21 days. Laboratory feed which was available commercially given to the mice. Animals were handled according to the ethical limitations of laboratory animal use.

Experimental Plan

The thirty (30) young albino rats with the weight of 150-200 grams were taken for research purpose from the animal station, Physiology department, GCUF. The male young albino rats were subjected to acclimatization at suitable environmental conditions of animal house temperature, and surrounding humidity (40 to 60%) for 21 days, routine diet, water intake and

medicine was available to animals, some ethical condition are including, on caring and use of animal model for the prevention of severe health related problems were taken on bio ethics committee Government College University Faisalabad, Pakistan was followed. Thirty (30) male young albino healthy rats were used and their duration of trial will be 21 days, six (n=6) rats were dissected on 0 day, before the start of study and the remaining 24 rats were equally divided in to 4 groups containing 6 rats in each group. They were fed standard diet and distilled water ad libitum. The illumination was maintained at 12-hour cycle of daylight and dark.

Experimental Design

Thirty-two male albino rats with a weight of 150-300 grams were taken and Rats were randomly divided into five groups (n=6). The first group was kept as a control group. The second group was kept as a positive group. The group numbers three and four were taken MgO nanoparticle administration via oral gavage. The dose given was 0.2mg/dL, 0.4mg/dL respectively. The doses were synthesized by addition of nanoparticles in distilled water. The group number five was kept as a standard group. They will be assigned the following abbreviations:

NCG = Negative control group (Healthy Rats); this group was throughout administrated with chow maintenance diet abbreviated as (CMD) and water. The number of rats was N=6

PCG = Positive control group (Acute lungs injury rats); this group was initially treated with CCl4 and then with Chow maintenance diet and water. (N=6)

SCG = Standard control group was initially administrated with CCl4 to induce injury and then treated with UDCA (Ursodeoxycholic acid) followed by Chow maintenance diet and water. (N=6)

LDTG = this group was initially administrated with CCl4 to induce injury and then treated with Magnesium oxide nanoparticle (MgO) in the concentration of 150 mg/kg/day followed by Chow maintenance diet and water. (N=6)

HDTG = this group was initially administrated with CCl4 to induce injury and then treated with Magnesium oxide nanoparticle (MgO) in the concentration of 300 mg/kg/day followed by Chow maintenance diet and water. (N=6)

The high and low dosage regimens of MgO nanoparticles given in the rat groups were based on previously reported optimal dosages in rats. In addition. Further corroboration carried out by undertaking an acute toxicity study of the selected nanoparticles.

Treatment Schedule

Drug administration and diet schedule in young albino rats of male sex for the experimental procedure of 0 to 21 days.

MgO nanoparticles characterization

Nanoparticles were characterized from the physics lab of GCUF by Scanning Electron Microscope SEM.

Manganese Oxide Nanoparticles Oral Administrations

Evaluation of the MgO nanoparticles' toxicity the toxicity of MgO nanoparticles at various concentrations was evaluated using the methods proposed by Irwin, 1968, and Kumari *et al.,* 2012. The results of the literature suggest that rats employed as experimental animals should receive of MgO nanoparticles at doses based on body weight. So In light of the recommended dosage: Based on the rats' body weights, the dose for the current study was chosen. First, the dose was established at one rat per day by taking into account the average body weight of the rats that would be used in the study. The dose was modified to account for both the total number of rats in the treatment group.

Physical Parameter

Measuring body weight

The body weight was measured by using analytic balance. From day 1 to the last day of trial, the weight of each rat was measured.

Dissection

Rats were dissected on the 21st day of experiment. Every rat was weighed prior to dissection. Rats were given anesthesia with IV injection of 100 mg/kg ketamine and 10 mg/kg xylaz and shifted to dissection tray one by one. Firstly, skin of rat was removed properly by starting from lower side of abdomen to the upper body parts via sharp scissors. When successive cuts were made, skin was raised by using dissecting forceps and slightly exposed the abdominal organs by tearing the muscle.

Liver function analysis

Blood samples were taken from each mouse by cardiac puncture method. Serum was then separated from blood by centrifugation and stored at -20°C for further use. These samples were subjected to LFT for following enzymes like ALP, ALT, AST and Bilirubin. Serum enzyme concentration was determined by the commercially available (Crescent® Diagnostic kit, by Jeddah, catalog # 15204C) kit method.

Histological examination

It was conducted by the routine protocol for pancreatic and liver tissue and with hematoxylin and eosin stain (H&E; Hasan *et al.,* 2018).

Lipid profile

Various parameters like Total cholesterol, Low density Lipoprotein, high density Lipoprotein and triglycerides were estimated in blood sample.

RESULTS AND DISCUSSION

MgO nanoparticles characterization

Scanning Electron Microscopy

The SEM (Nova Nano, scanning electron microscope-450) elucidated the formation of rhomboid magnesium oxide nanoparticles.

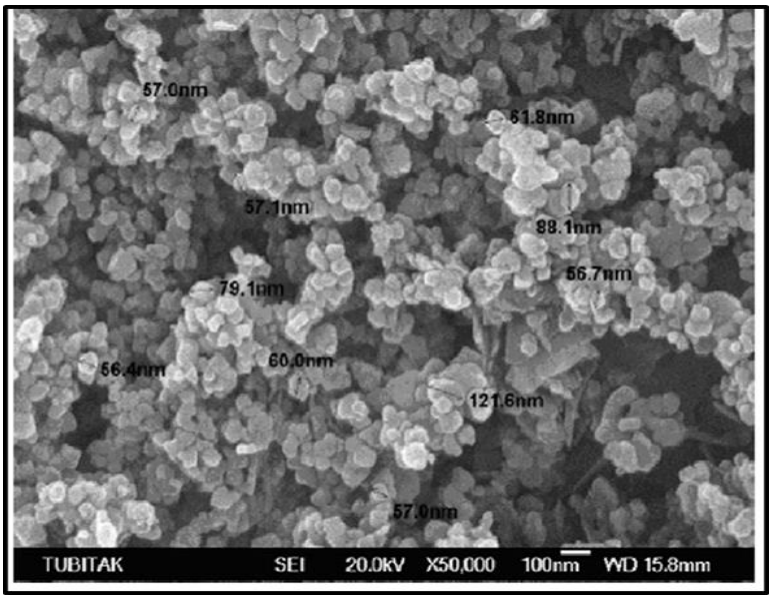


Figure 1: SEM of magnesium oxide MgO

Physical Parameter

Body Weight

The increase or decrease in mean body weight of each group was evaluated i.e. at day l, day 7, day 14 and day 21. The positive control group showed a statistically significant reduction in mean body weight ($P<0.05$). The Standard Control Group (SCG) exhibited an increase in the mean body weight ($P<0.05$). A significant increase in mean body weight was recorded in the NCG groups following a phase of initial increase ($P<0.05$) but it was not as significant as in High dose treatment group groups initial decrease ($P>0.05$).

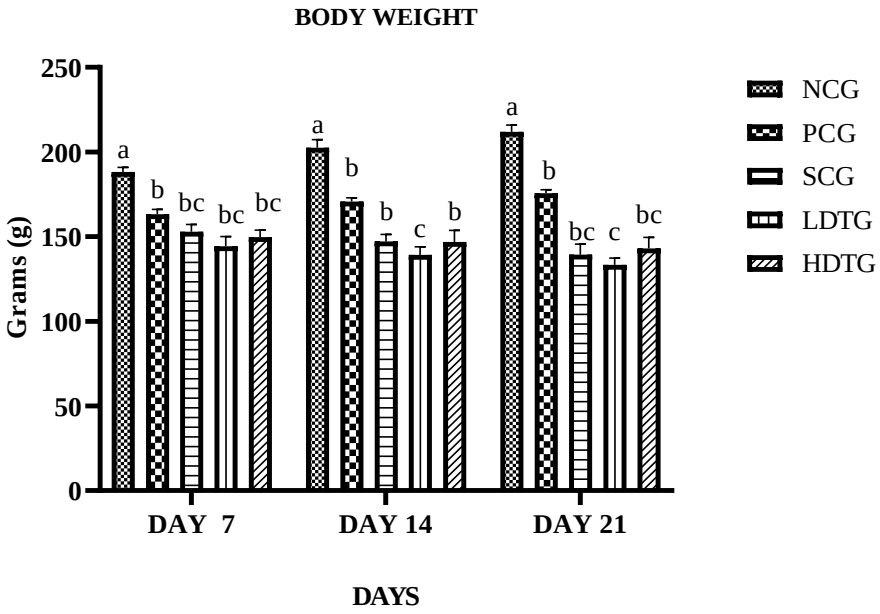


Fig 2: Body weight (in grams) of the Standard Control Group (SCG), Low Dose Treatment Group (LDTG), High Dose Treatment Group (SCG), magnesium oxide low dose at 150 mg/dL and magnesium oxide high dose group at 300 mg/dL in a rat model

Serum Analysis

Concentration of different enzymes was estimated by Liver Functioning Test to check the hepatoprotective potential. LFT report gave a comparative analysis between CCl4 treated group and MgO treated group on the basis of levels of enzymes in serum. The concentration of all enzymes was significantly decreased in treatment groups as compared to the PC group (Figure 2; P≤0.05). The aspartate aminotransferase was found to be significantly increased in PC group as compared to LGTG and HDTG i.e., 75.19±3.76a as opposed to 62.89±2.75b and 36.23±2.72c respectively (p<0.05). It was observed that the mean concentration of AST in treatment groups decreased (Figure 2; p<0.05). The mean concentration of ALT significantly decreased in treated groups, e.g., LDT and HDT group, as compared to the positive control group (PCG).i.e., 101.24±3.98b and 53.34±2.97c as compared to 154.53±5.72a respectively. The ALP was found to be significantly increased in PC group as compared to LGTG and HDTG i.e., 19.36±1.94d as opposed to 23.76±1.23c and 42.34±1.68b respectively (p<0.05). The mean concentration of BIL significantly decreased in treated groups, e.g., LDT and HDT group, as compared to the positive control group (PCG) i.e., 0.95±0.22b and 0.79±0.20c as opposed to 1.78±0.17a.

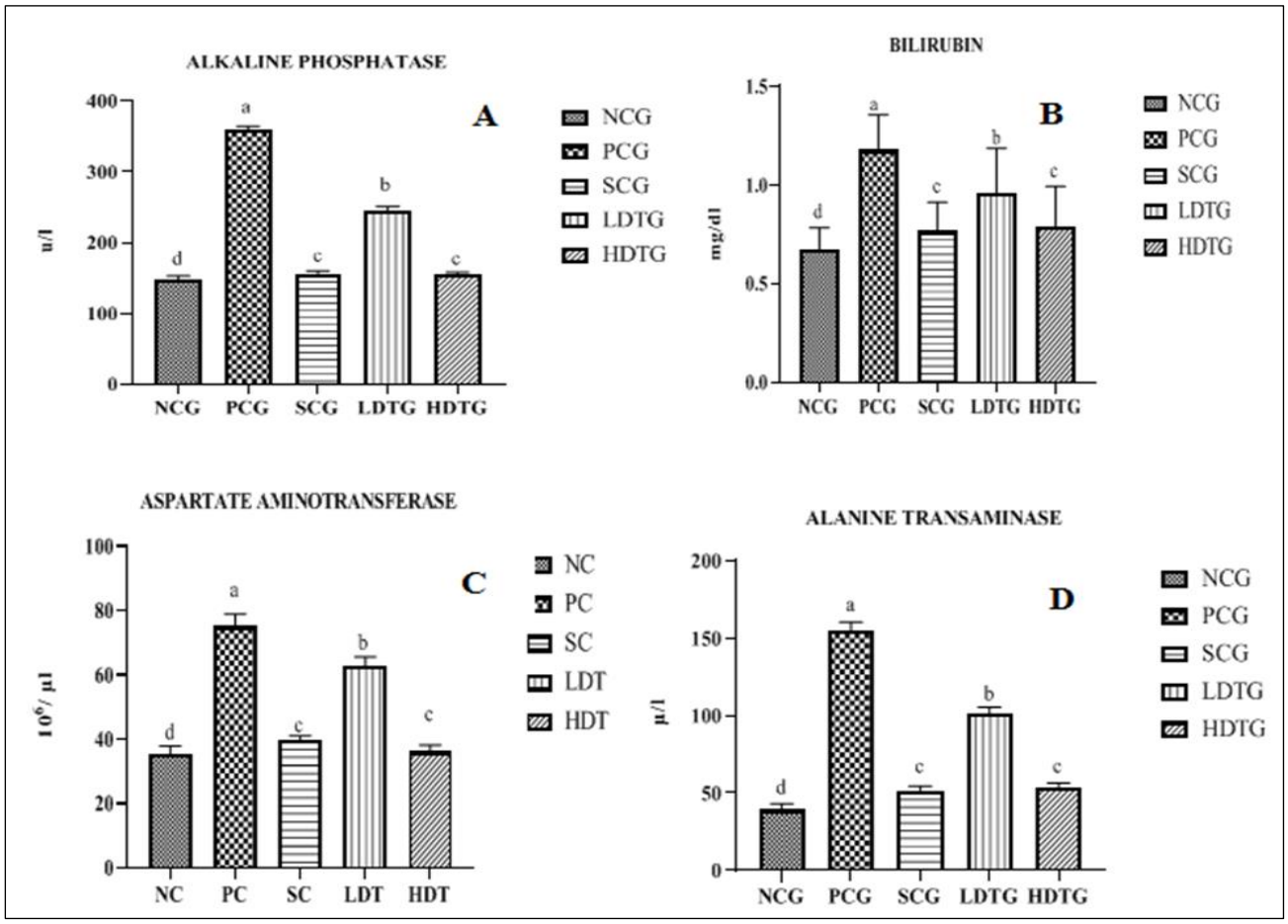


Figure: 3 Effect of MgO nanoparticles on serum conc. of ALP, BIL, AST, ALT

Results are means ± SE. NCG (negative control), PCG (positive control), SC (standard control), LDTG (low dose treated group), HDTG (high dose treated group). This means values having different superscripts are significantly different from each other (P≤0.05).

Lipid Profile

The level of total cholesterol (TC) was significantly decreased in treatment groups as compared to the PC group (figure 3; P≤0.05). Mean serum TC level was decreased in groups treated with polyherbal formulation LDTG and HDTG as compared to the PC group, i.e. 61.67±3.87, 40.65±2.79 as opposed to 68.8±5.48 (Figure 3; P≤0.05). The values of concentrations of HDL-Chol were significantly increased in treatment groups as compared to the PC group i.e., 23.76±1.23and 42.34±1.68for LDTG and HDTG as opposed to 19.36±1.94 (Figure 3; P≤0.05). ANOVA analysis of LDL-Chol levels among different groups revealed a significant decrease in treatment groups as compared to the PC group, i.e., 63.24±4.98 and 49.78±2.97 for LDTG and HDTG as opposed to 69.53±5.82 for PC group (Figure 3; P≤0.05).

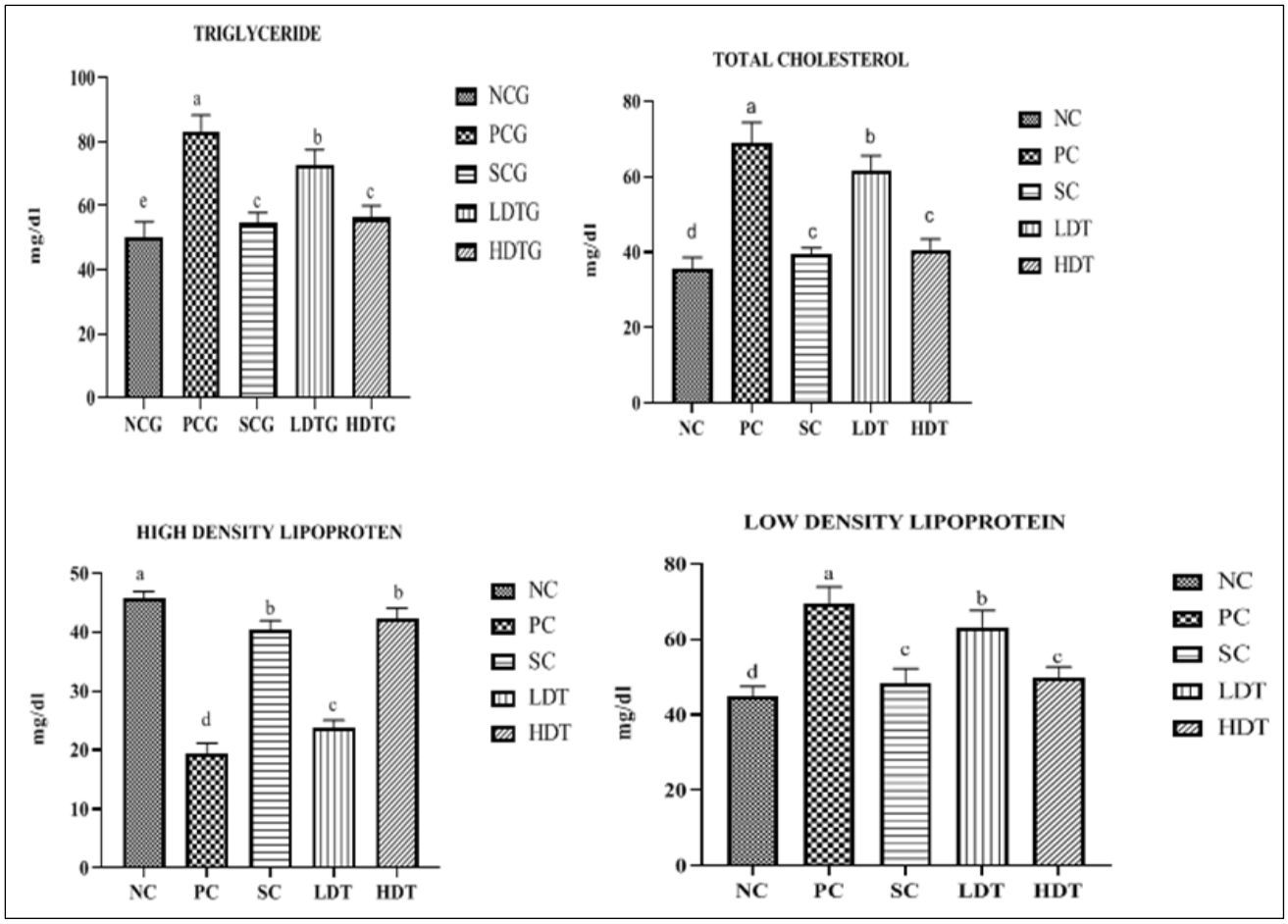
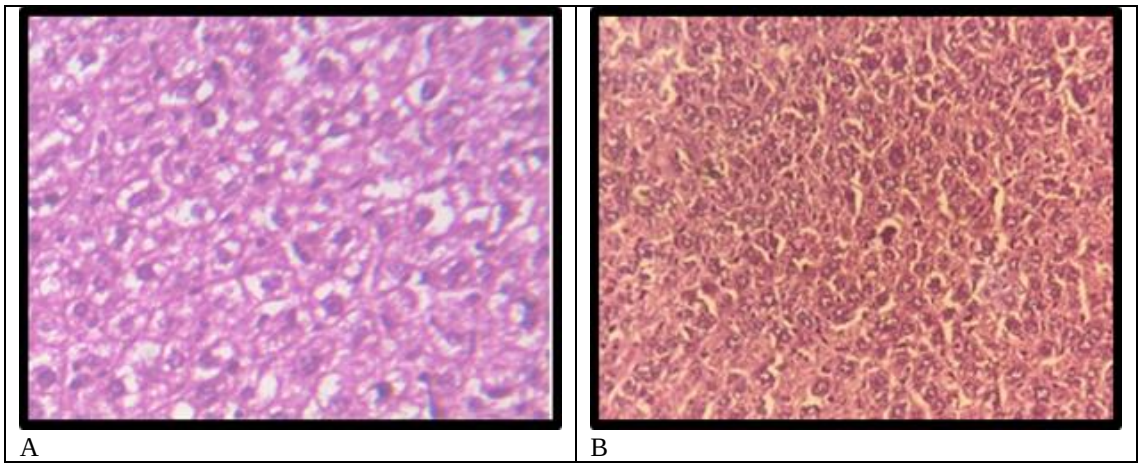


Figure 4: Effect of MgO on serum concentration of TC (5A; mg/dl), HDL (5.B), TG (5.C), and LDL (5.D)

Results are means ± SE. NCG (negative control), PCG (positive control), SC (standard control), LDTG (low dose treated group), HDTG (high dose treated group). This means values having different superscripts are significantly different from each other (P≤0.05).

Histological Examination

A significant difference was noteworthy between negative control and positive control. The positive control showed a noteworthy degeneration of hepatocytes (Figure 4B). Group A, the negative control indicated normal morphology of hepatocytes (H&E; Magnification at 40X; Figure 4A). Standard control group (SCG) shows that hepatocytes did not undergo degeneration (Figure 4C). Low dose treated group (LDTG) shows that hepatocytes did not undergo degeneration (Figure 4D). High dose treated group (HDTG) shows that hepatocytes did not degenerate.



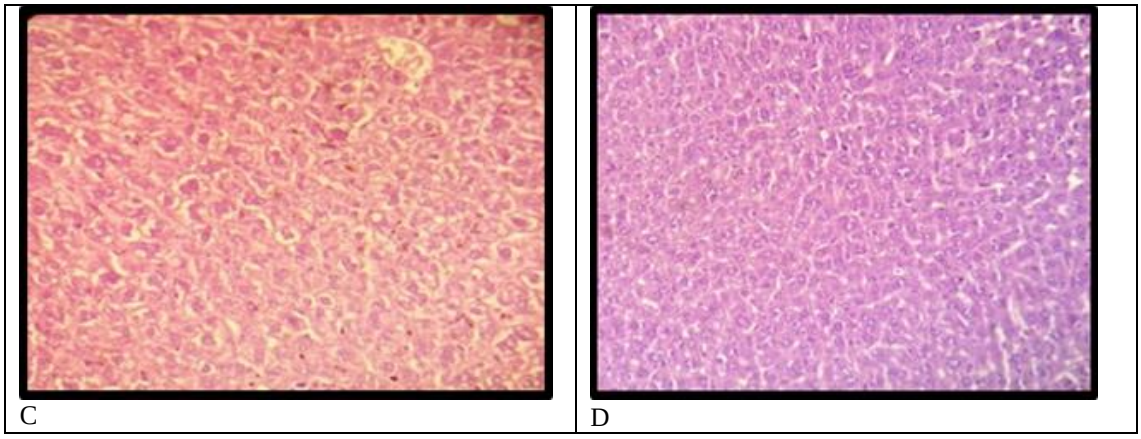


Figure 5: Histology of Liver tissue samples, negative control (4A), positive control (4B), Standard control (4C); low dose treated group (4D)

Some of the individuals had no hemorrhages in the right hypochondrium's subcutaneous tissues, thoracic muscles, or abdominal muscles. Given biomechanics, it is unclear why blunt liver injuries happen and why the rib cage protects the abdomen from impact injuries in such circumstances (Shao *et al*., 2013). The current study investigated that the MgO nanoparticles of a significant, time-dependent, and consistent role in reducing liver injury. The current inspection showcased that body weight was gained on the 14th day of the experiment. Significant weight gain was observed in groups MDC and HDE in contrast to LDE and treated groups. Dropped body weight in liver injury could be due to decreased tissue proteins and increased muscle hypotrophy (Cheng *et al*., 2013). This finding is analogous to Thilagam *et al*., (2018) that showed an increased body weight within 21 days liver injury rats treated by MgO nanoparticles. Another study demonstrated body weight gain in liver injury rats treated with the MgO nanoparticles (Qureshi *et al*., 2019).

Hematological indicators significantly improved as a result of the current examination. Improvement in the concentration of HCT and HGB in RBCs in the LDTG and HDTG therapy groups in comparison to liver damage. The mean PLT concentration was higher in the liver injury groups, and it was considerably lower after the NP treatment. Hematological markers in liver damage are significantly impacted by hyperglycemia. Disturb cellular metabolism, which causes changes in cellular structure and activities (Bergmann & Sypniewska, 2013). According to a study, the nanoparticle MgO increased the concentration of RBCs, HGB, and HCT in liver injury rats. According to a 2012 study by Asgary *et al*., NS aqueous extract improved RBC and HGB levels in liver injury. Increased RBC and HGB counts were seen in several trials (Qureshi *et al*., 2019). The treatment and management of liver injury involve several components. These are pharmacotherapy, eating habits, and appropriate exercise. In terms of pharmacotherapy, nanoparticle magnesium oxide is widely used for liver injury treatment. It can modify the constitution of liver cells. Magnesium oxide elicit the inhibition of and they used in liquids form mix in normal saline water and orally gavage to rats and calculated amount of magnesium oxide provide to rats according the body weight.

According to a different study, the liver injury group's RBC count, HGB concentration, and HCT level were all lower (Ezenwaka *et al*., 2008). Reduced RBC count may be caused by prolonged liver damage to RBC membrane proteins, which results in morphological alterations and accelerated RBC aging (Letcia *et al*., 2017). (Cawood *et al*., 2006) According to a different study, liver damage eventually causes the body's RBC count to drop (Cawood *et al*., 2006). When there is liver damage, HGB levels rise and create glycosylated HGB, which lowers the level of total HGB (Alamri *et al*., 2019). According to research, liver damage decreased HGB levels, which in turn affected RBC's ability to carry oxygen and failed to meet their physiological requirements, leading to liver problems (Thomas, 2007).

The current studies showed increased WBC counts in liver damage, whereas decreased WBC counts were seen in the NP-treated groups. WBC count increased with liver injury; oxidative stress may be to blame showed that NP is efficient in lowering WBC and platelet counts in liver damage. According to certain research, liver damage patients had higher PLT counts than the healthy group. Increased PLT count adhesiveness under the liver damage situation may be caused by a number of factors, such as perhaps decreased acute liver injury (Colwell & Nesto, 2003) shown that NS oil has a suppressive effect on PLT and nanoparticle of magnesium oxide more effective (Ali & Blunden, 2003).

Lipidic factor after receiving NP therapy, HDL analysis revealed increased levels at both LDTG and HDTG. High dosage nanoparticles were more effective than low dose extract in raising HDL levels. An improved lipid profile is related to a healthy liver. As more fatty acids are stored in the liver for use as energy

and to be transformed into triglycerides, liver damage may result in incorrect outcomes that could raise triglyceride levels (Shih *et al*., 1997). According to some studies, the number of LDL receptors increases in a physiological state, and a long-term liver injury deficit may be caused by a decrease in the number of LDL receptors, which increases the amount of LDL particles in the blood and, as a result, the level of LDL cholesterol in the liver injury (Suryawanshi *et al*., 2006). According to Kaur *et al*, magnesium oxide nanoparticle therapy significantly reduced total cholesterol, triglycerides, and LDL. Reduction in lipid markers indicates that been improved. The current investigation revealed an increase in HDL characteristics and a decrease in total cholesterol, triglycerides, and LDL. In comparison to liver injury rats that were not given MgO nanoparticle treatment, the serum HDL level was dramatically raised in the PHF-treated diabetic rats. Significantly lower cholesterol levels following treatment compared to the liver injury group in the HDTG and LTGD groups. Comparing the current research group to the CCL4-induced diabetes group, it was found that triglyceride and LDL levels were lower. Elevated lipid liver injury causes deteriorating alterations in the liver enzymes. Increase lipid often concerned with the progress of liver damage. It also has been illustrated that xenobiotic liver microsomes are tremendously sensitive to lipid peroxidation. Thus, the elevated lipid peroxidation causes corrosion of the liver and may provoke hepatocellular damage (Noureddin & Rinella, 2015). Nanoparticle magnesium oxide reportedly decreased the level of AST and ALT in the liver enzymes. Current findings are similar with (Dollah *et al*., 2013; Gaur, 2015) it was witnessed that nanoparticles exhibit hepatoprotective effects due to their active constitutes such as (Asadi-Samani *et al*., 2015). Reduction in liver enzymes signifies the ameliorating effect on hyperglycemia (Feldman *et al*., 2020).

CONCLUSION

MgO nanoparticle inoculation at standard, low, and high doses was safe and effective, with no side effects. It would be interesting to look at the histological and cellular changes that occur at exceedingly high MgO nanoparticle doses. In addition, further research will be intriguing in elucidating the accumulation, deposition, and excretory processes of MgO nanoparticles.

REFERENCES

- Abedi, A., Azarnia, M., & Golestani, S. (2016). Effect of Different Times of Intraperitoneal Injections of Human Bone Marrow Mesenchymal Stem Cell Conditioned Medium on Gentamicin-Induced Acute Kidney Injury. *Urology Journal*, *13*(3), 2707-2716.
- Ayobian-Markazi, N., Fourootan, T., & Zahmatkesh, A. (2014). An in vitro evaluation of the responses of human osteoblast-like SaOs-2 cells to SLA titanium surfaces irradiated by erbium: yttrium–aluminum–garnet (Er: YAG) lasers. *Lasers in medical science*, *29*, 47-53.
- Du, Z., Wei, C., Cheng, K., Han, B., Yan, J., Zhang, M., ... & Liu, Y. (2013). Mesenchymal stem cell–conditioned medium reduces liver injury and enhances regeneration in reduced-size rat liver transplantation. *Journal of Surgical Research*, *183*(2), 907-915.
- Eini, F., Foroutan, T., Bidadkosh, A., Barin, A., Dehghan, M. M., & Tajik, P. (2012). The effects of freeze/thawing process on cryopreserved equine umbilical cord blood-derived mesenchymal stem cells. *Comparative Clinical Pathology*, *21*, 1713-1718.
- Ferrer, L., Kimbrel, E. A., Lam, A., Falk, E. B., Zewe, C., Juopperi, T., ... & Hoffman, A. (2016). Treatment of perianal fistulas with human embryonic stem cell-derived mesenchymal stem cells: a canine model of human fistulizing Crohn's disease. *Regenerative medicine*, *11*(1), 33-43.
- Foroutan, T., Ahmadi, F., Moayer, F., & Khalvati, S. (2020). Effects of intraperitoneal injection of magnetic graphene oxide on the improvement of acute liver injury induced by CCl4. *Biomaterials Research*, *24*(1), 1-9.
- Foroutan, T., Nafar, M., & Motamedi, E. (2020). Intraperitoneal injection of graphene oxide nanoparticle accelerates stem cell therapy effects on acute kidney injury. *Stem Cells and Cloning: Advances and Applications*, 13, 21-32.
- Foroutan, T., Amid, R., & Karimi, M. R. (2013). Comparison of manual tools, ultrasonic and erbium-doped yttrium aluminum garnet (Er: YAG) laser on the debridement effect of the surface of the root of teeth suffering from periodontitis. *Journal of lasers in medical sciences*, *4*(4), 199.
- Fu, Y., Zheng, S., Lin, J., Ryerse, J., & Chen, A. (2008). Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. *Molecular pharmacology*, *73*(2), 399-409.
- Kopp, J. L., Grompe, M., & Sander, M. (2016). Stem cells versus plasticity in liver and pancreas regeneration. *Nature cell biology*, *18*(3), 238-245.
- Luo, L., Ma, Y., Zheng, Y., Su, J., & Huang, G. (2022). Application progress of organoids in colorectal cancer. *Frontiers in Cell and Developmental Biology*, *10*, 815067.
- Lin, F., Moran, A., & Igarashi, P. (2005). Intrarenal cells, not bone marrow–derived cells, are the major source for regeneration in postischemic kidney. *The Journal of clinical investigation*, *115*(7), 1756-1764.
- Lin, F., Cordes, K., Li, L., Hood, L., Couser, W. G., Shankland, S. J., & Igarashi, P. (2003). Hematopoietic stem cells contribute to the regeneration of renal tubules after renal ischemia-

reperfusion injury in mice. *Journal of the American Society of Nephrology*, *14*(5), 1188-1199.

- Lotfinia, M., Kadivar, M., Piryaei, A., Pournasr, B., Sardari, S., Sodeifi, N., ... & Baharvand, H. (2016). Effect of secreted molecules of human embryonic stem cell-derived mesenchymal stem cells on acute hepatic failure model. *Stem cells and development*, *25*(24), 1898-1908.
- Li, M., Gong, J., Gao, L., Zou, T., Kang, J., & Xu, H. (2022). Advanced human developmental toxicity and teratogenicity assessment using human organoid models. *Ecotoxicology and Environmental Safety*, *235*, 113429.
- Nayak, T. R., Andersen, H., Makam, V. S., Khaw, C., Bae, S., Xu, X., ... & Ozyilmaz, B. (2011). Graphene for controlled and accelerated osteogenic differentiation of human mesenchymal stem cells. *ACS nano*, *5*(6), 4670-4678.
- Neve, R. L., Harris, P., Kosik, K. S., Kurnit, D. M., & Donlon, T. A. (2000). Identification of cDNA clones for the human microtubule-associated protein tau and chromosomal localization of the genes for tau and microtubule-associated protein. *Brain Res*, 387, 271-301.
- Paganelli, A., Tarentini, E., Benassi, L., Kaleci, S., & Magnoni, C. (2020). Mesenchymal stem cells for the treatment of psoriasis: a comprehensive review. *Clinical and Experimental Dermatology*, *45*(7), 824-830.
- Parekkadan, B., van Poll, D., Suganuma, K., Carter, E. A., Berthiaume, F., Tilles, A. W., & Yarmush, M. L. (2007). Mesenchymal stem cell-derived molecules reverse fulminant hepatic failure. *PloS one*, *2*(9), e941.
- Park, J., Kim, B., Han, J., Oh, J., Park, S., Ryu, S., ... & Kim, B. S. (2015). Graphene oxide flakes as a cellular adhesive: prevention of reactive oxygen species mediated death of implanted cells for cardiac repair. *ACS nano*, *9*(5), 4987-4999.
- Salehi, P. M., Foroutan, T., Javeri, A., & Taha, M. F. (2017). Extract of mouse embryonic stem cells induces the expression of pluripotency genes in human adipose tissue-derived stem cells. *Iranian journal of basic medical sciences*, *20*(11), 1200.
- Sánchez, L., Gutierrez-Aranda, I., Ligero, G., Rubio, R., Muñoz-López, M., García-Pérez, J. L., ... & Menendez, P. (2011). Enrichment of human ESC-derived multipotent mesenchymal stem cells with immunosuppressive and anti-inflammatory properties capable to protect against experimental inflammatory bowel disease. *Stem cells*, *29*(2), 251-262.
- Solanki, A., Chueng, S. T. D., Yin, P. T., Kappera, R., Chhowalla, M., & Lee, K. B. (2013). Axonal alignment and enhanced neuronal differentiation of neural stem cells on graphene-nanoparticle hybrid structures. *Advanced materials (Deerfield Beach, Fla.)*, *25*(38), 5477.
- Tao, Y. C., Wang, M. L., Chen, E. Q., & Tang, H. (2018). Stem cells transplantation in the treatment of patients with liver failure. *Current stem cell research & therapy*, *13*(3), 193-201.
- Van Poll, D., Parekkadan, B., Cho, C. H., Berthiaume, F., Nahmias, Y., Tilles, A. W., & Yarmush, M. L. (2008). Mesenchymal stem cell–derived molecules directly modulate hepatocellular death and regeneration in vitro and in vivo. *Hepatology*, *47*(5), 1634-1643.
- Volarevic, V., Nurkovic, J., Arsenijevic, N., & Stojkovic, M. (2014). Concise review: therapeutic potential of mesenchymal stem cells for the treatment of acute liver failure and cirrhosis. *Stem cells*, *32*(11), 2818-2823.
- Wang, X., Kimbrel, E. A., Ijichi, K., Paul, D., Lazorchak, A. S., Chu, J., ... & Xu, R. H. (2014). Human ESC-derived MSCs outperform bone marrow MSCs in the treatment of an EAE model of multiple sclerosis. *Stem cell reports*, *3*(1), 115-130.
- Wang, Y. H., Wu, D. B., Chen, B., Chen, E. Q., & Tang, H. (2018). Progress in mesenchymal stem cell–based therapy for acute liver failure. *Stem Cell Research & Therapy*, *9*, 1-9.
- Gadkari, R., Zhao, L., Teklemariam, T., & Hantash, B. M. (2014). Human embryonic stem cell derived-mesenchymal stem cells: an alternative mesenchymal stem cell source for regenerative medicine therapy. *Regenerative medicine*, *9*(4), 453-465.