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Short and Long Term Administration of Gold Nanorods Induces Hepatic and Renal Toxicities in Male Albino Rats

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Abstract

Gold nanoparticles are known by its good penetrating ability and translocation into cells. Despite their convenience, they can induce biochemical abnormalities and tissue toxicity. This study aimed to investigate the possibility of hepato-renal toxicities induced by gold nanorods (AuNRs) on liver and kidney tissues at short and long term basis. The experimental design was subdivided into short term study (AuNRs 300 µg/kg body weight i.p) and long term study (AuNRs 30 µg/kg body weight i.p), where adult male albino rats were used and allocated into two equal groups. The first group received IP injection of normal saline 0.9% and the second group received AuNRs. At the end of the experiment, five animals from each group were sacrificed and blood was collected on plain test tubes for biochemical study. Liver and kidney tissues were collected from both groups, and preserved a buffered formalin solution for histopathological examination. The high dose of gold nanorods induced a significant increase in Oxidant enzymes and liver and kidney function as well as degeneration and necrotic changes corresponding to control group. It has been concluded that short and long term intraperitoneal administration of gold nanorods adversely affected the biochemical and hepatorenal histomorphological architecture.

Keywords: Gold nanorods • Histopathology • Kidney • Liver • Male albino rats

Introduction

In the late 1970s, nanoparticles belonged to biomedicine and now about 10,000 publications are being published annually [1]. Up until recently, nanoparticles are being developed for its medical applications to treat serious diseases e.g. cancer due to its higher selectivity. They are modified and coated with different carriers to overcome its disadvantage of being hydrophilic and to facilitate its translocation into cells e.g. polymer nanocapsules, polymer-protein conjugates, albumin-drug conjugates, block-copolymer micelles, gold nanoparticles coated with Polyethylene glycol (PEG) and anti-microbial silver nanoparticles [2]. Nowadays, the field of nanomedicine has been developed to enhance the targeted drug delivery of including metal nanoparticles. Even though this type of nanoparticles is convenient, they are hazardous. This in turn can induce toxicity, inefficient entry into cells and clearance from tissues or organs. These barriers can be broken by functionalization of gold nanoparticles (AuNPs) with poly ethylene glycol (PEG). This type of nanoparticles has presented low cytotoxicity and excellent delivery [3]. Gold nanorods are one of the forms of gold nanoparticles, is featured by its good penetrating ability and tissue uptake [4, 5]. The objective of this study is to evaluate the possibility of gold nanorods to induce alteration in the oxidant and anti-oxidant enzymes and to induce alterations in the biochemical functions and in the histopathological architecture of liver and kidney tissue, and to establish the resultant adverse effect of the gold nanorods on the normal liver and kidney tissues.

Material and Methods

Synthesis of gold nanorods (AuNRs)

Here is a diagram showing the steps [6] **(Figure 1)**.

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Characterization of GNRs

A Spectrophotometer V-630 UV-VIS (Jasco, Japan) was used to measure the absorption spectra of GNRs solutions. Transmission electron microscopic (TEM) (JEOL JEM 2010) images were operated at 100 kV accelerating voltage. From the TEM results, it is confirmed that most of the nanoparticles made have rod shapes with the long to the short axis length ratio of ~ 4 and thus absorb the light at ~700 nm in **Figure 2**.

Animal's Ethical approval: ZU/IACUC number: *ZU-IACUC/2/F/49/2018* from IACUC committee of Zagazig University, Egypt**.** Sixty adult male albino rats weighing 200-250gm were used. They were obtained from the laboratory animal house of the faculty of veterinary medicine, Zagazig University. They were left to acclimatize in the laboratory of pharmacology for one week. They were given clean tap water *ad libitum* and balanced ration.

Experimental design

Experiment I (short term study): Forty eight adult male albino rats were allocated into two equal groups, each of twenty four. The first group was left as a control, injected with normal saline 0.9% i.p and the second group was injected with AuNRs 300 µg/kg b.wt (10 nm) i.p dissolved in normal saline [7]. On days one, three, seven and fourteen post treatment, six animals from each group were sacrificed and blood samples were collected in clean & dry test tubes & left in a slope position to coagulate at ambient temperature for 45 minutes. Serum was then separated and centrifuged at 3000 rpm for 10 minutes. Clear serum was transferred carefully into clean & dry vials & kept frozen at -20°C until analyzed for biochemical parameters including liver function test (ALT, AST, albumin and ALP), kidney function test (Urea and Creatinine), Oxidant & Anti-oxidant enzymes (SOD, catalase, GPX and MDA). Liver and kidneys were collected from both groups and kept in a jar containing 10% neutral formalin for histopathological examination.

Experiment II (Long term study): Twelve adult male albino rats were allocated into two equal groups; six rats of each. The first group was left as a control, injected normal saline 0.9% i.p injection and the second group was injected AuNRs 30 µg/kg b.wt (10 nm) i.p dissolved in normal saline [8] for five consecutive days in the first month (from day one to day five). The same dose was injected from day thirty-one to day thirty-five. On day sixty, rats of both groups were sacrificed and the same procedure of experiment I was adopted.

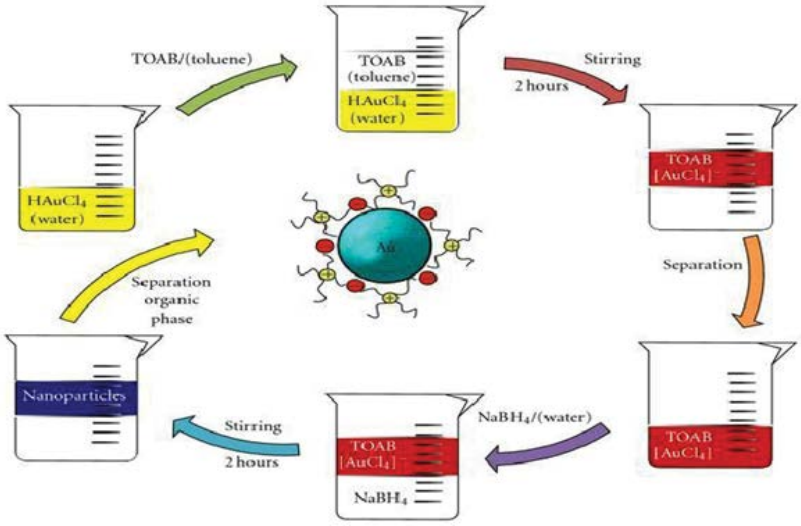

Figure 1: Synthesis of gold nanorods (AuNRs).

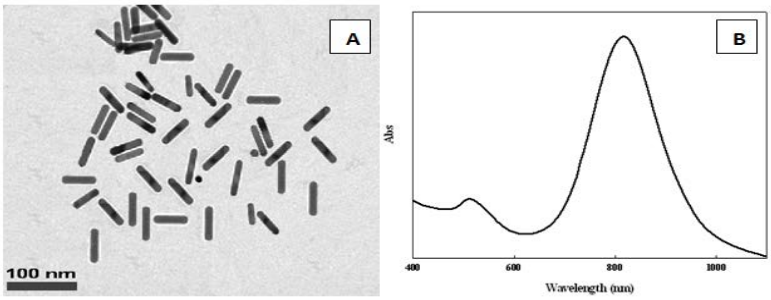

Figure 2: Electron microscopic shape of gold nanorods TEM images (A), and absorption spectra of aqueous of 10nm AuNRs solution (B).

1) Biochemical analysis:

A biochemical autoanalyzer (Type 7170, Hitachi) was used to measure serum levels of aspartate aminotransferase (AST), gamma-glutamyl transferase(GGT), alanine transaminase(ALT) and alkaline phosphatase (ALP) were measured; while to evaluate the kidney function, the levels of urea (UREA) and creatinine (CREA) were measured.

2) Oxidant/ Antioxidant parameters: Estimation of the SOD and GPX activity were performed and calculated according to the manufacturer's instruction (Ransod-Randox Lab, Antrim, UK) and expressed as U/mL [9, 10].

Serum CAT was measured according to the method proposed by (Aebi 1984) [11]. In a UV range, H2O2 shows a higher absorption with lowered wavelength. Variation in absorbance (DA240) per unit time is a measure of CAT activity. The CAT activity is measured in specific units/milligram. One unit of CAT corresponds to the amount of enzyme needed to decompose H2O2 in phosphate buffer, at pH 7.0, in 1 sec of reaction. MDA levels were analyzed spectrophotometrically [12]. Serum amount was incubated at 37 °C in a metabolic shaker for 2 h. One milliliter of 10% (w/v) trichloro acetic acid was mixed with homogenate followed by centrifugation at 3000 rpm for 10 min. Aliquots (1 mL) of the clear supernatant were mixed with 1 mL of 0.67% (w/v) 2-thiobarbituric acid and placed in a boiling water bath for 10 min, cooled and diluted with 1 mL distilled water. The absorbance of the solution was recorded at 535 nm, and the concentration of MDA was calculated using tetra ethoxypropane as an external standard.

3) Statistical analysis: Independent T- test followed by **Levene's Test** Significant Difference (**Levene's** HSD) test as post hoc test were used [13]**.** Analysis was done using Statistical Package version 22.0 (IBM Corp., Armonk, NY, USA). Results were presented as means ± SEM (Standard Error of Mean). The value of $P < 0.05$ was used to indicate statistical significance

4) Histopathological study: The preserved liver and kidney tissues were processed in an automated tissue processor. Paraffin sections (4–5 um) were stained with hematoxylin and eosin**.** Stained sections were examined for inflammatory reactions, degenerative, necrotic, apoptotic changes and any other pathological lesions in the examined tissues of experimental rats [14].

Results

1) Effects of intraperitoneal injection of AuNRs 300 µg/ kg bwt 10nm on hepatic of male rats on Days-1, 3, 7 and 14 post injections

On 1st, 7th, and 14th day post treatments, gold nanorods induced a significant rise of ALT of AuNRs treated rats as compared to control group, although no significant change occurred on the third day post treatment. It was found that AST value of AuNRs taking rats, increased significantly on 1st, 7th, and 14th day post injection; while no significant change on day three post injection. Also, it was illustrated that the serum ALP value of GNRs treated group increased in a significant manner on day three, seven and fourteen day post treatments corresponding to control group, no significant change occurred on day one post treatment. The gold nanorods didn't cause any change in serum albumin during the entire period of the study but a significant decrease on day three post treatment as compared to control group as shown in **Table 1.**

2) Effects of intraperitoneal injection of AuNRs 300 µg/ kg bwt 10nm on hepatic of male rats on day 60 post injection

A significant rise in the value serum ALT, AST and ALP associated with significant decrease in the value serum albumin occurred as shown in **Table 2**.

3) Effects of intraperitoneal injection of AuNRs 300 µg /kg bwt 10 nm on renal function parameters of male albino rats on 1st, 3rd, 7th, and 14th day post injection

It was shown that the serum urea and creatinine of GNRs taking group

Table 1: Effects of intraperitoneal injection of AuNRs 300 µg/ kg bwt 10nm on some liver function parameters of male rats on Days-1, 3, 7 and 14 post injection.

	1d		3d		7d		14d	
	Control	GNRs	Control	GNRs	Control	GNRs	Control	GNRs
ALT	24.93 ± 0.55	30.96 ± 0.39*	20.23 ± 0.59	20.56 ±1.59	23.38 ± 0.72	26.35 ± 0.81*	21.48 ± 0.52	27.88 ± 0.41*
AST	13.73 ± .29	19.06 ± 0.41*	17.11 ± 0.35	17.31 ± 0.50	16.30 ± .37	14.30 ± 0.25*	14.58 ± 0.30	21.55 ± 0.45*
ALP	355.33 ± 1.60	355.83 ± 1.96	108.5 ± 0.76	257.7 ± 1.28	196 ± 1.06	225.33 ± 1.05	312.17 ± 0.83	353.67 ± 1.2
Albumin	3.76 ± 0.04	3.73 ± 0.07	4.93 ± 0.25	3.92 ± 0.05*	3.95 ± 0.01	3.67 ± 0.06	3.52 ± 0.03	3.67 ± 0.07
Data represent means ± SE (n=6), * P<0.05 versus control.								

Table 2: Effects of intraperitoneal injection of AuNRs 300 µg/ kg bwt 10nm on some liver function parameters of male rats on Day 60 post injection.

	Day 60	
	Control	GNRs
ALT	33.50 ± 2.14	61.50 ± 2.71
AST	20.50 ± 1.69	73.50 ± 2.43
ALP	114.5 ± 1.15	266.5 ± 1.02
Albumin	4.34 ± 0.14	2.38 ± 0.10
Data represent means ± SE (n=6), * P<0.05 versus control.		

Table 3: Effects of intraperitoneal injection of AuNRs 300 µg/ kg bwt 10nm on renal functions of male rats on 1st, 3rd, 7th, and 14th day post injections.

	1d		3d		7d		14d	
	Control	GNRs	Control	GNRs	Control	GNRs	Control	GNRs
Urea	30.82 ± 0.45	46.6 ± 1.37	25.93 ± 0.99	42.18 ± 1.57	26.92 ± 0.53	43.06 ± 0.87	29.20 ± 0.59	45.93 ± 0.69
Creatinine	1.00 ± .016	1.76 ± .093	.88 ± .03	1.49 ± .08	0.92 ± 0.02	2.00 ± 0.05	0.79 ± 0.02	1.92 ± 0.02

increased significantly corresponding to control group along the course of the study **(Table 3)**.

4) Effects of intraperitoneal injection of AuNRs 30 µg/kg 10nm on renal function parameters of male albino rats on 60th day post injection

Table 4 showed a significant increase in the serum value of urea and creatinine occurred on day 60 post intraperitoneal injection

5) Effects of intraperitoneal injection of AuNRs 300 µg /kg bwt 10nm on oxidant and anti-oxidant enzymes of male rats on 1st, 3rd, 7th and 14th day post injection.

It was illustrated from Table 5 that the value of serum CAT of GNRs taking rats increased significantly on the first day post treatment, but declined on day three and seven post treatment in comparison with control group. The same dose of GNRs didn't cause any change in serum CAT on day fourteen post treatment. Also, dose of GNRs caused a significant increase in serum MDA value after one and three days post treatment as compared to control group, but no significant change occurred on the fourteenth day post treatment. On day one post treatment, the intraperitoneal administration of 300µg/kg b.wt induced sudden drop in serum SOD corresponding to the control, but the same dose caused abrupt increase in serum SOD on day three and fourteen post treatments. No significant change occurred on day seven post treatment **(Table 5)**.

A significant decrease in serum GPX of GNRs receiving group occurred on the first and third day post treatment parallel to the control group. The serum GPX value of the same group increased in a significant manner in comparison with the control group on the fourteenth day post treatment. No significant change on day seven post treatment.

6) Effects of intraperitoneal injection of AuNRs 30 µg /kg bwt 10 nm on oxidant and anti-oxidant enzymes of male albino rats on day 60 post treatments.

It was found on table 6 that the 30µg/kg bwt of GNRs decreased the serum value of CAT, SOD and GPX in a significant manner on day 60 post treatment. The same dose caused a significant increase in serum MDA on day 60 post treatment **(Table 6)**.

Table 4: Effects of intraperitoneal injection of AuNRs 30 µg/ kg bwt 10nm on renal function of male albino rats on 60th day post injection.

	60d	
	Control	GNRs
Urea	25.00 ± 1.57	64.00 ± 4.35*
Creatinine	0.75 ± 0.03	2.10 ± 0.13*
Data represent means ± SE (n=6), * P<0.05 versus control		

Histopathological results

Control group: All the examined organs during these periods (days 1, 3, 7, 14 and 60 post injection) including Liver and Kidneys revealed normal histo-morphological structures with preserved parenchymal functional units and fibrous stromal frameworks. Illustrative figure for the differently examined organs present in **Figure 3**.

Figure 4. Effect of intraperitoneal administration of AuNRs 300µg/kg bwt 10 nm on liver and kidney tissues of male albino rats on days-1 and 3 post treatments:

Examined sections from Kidney denoted cystic renal tubules particularly in the medulla and a few degenerative changes in some of the proximal tubular epithelium. Liver sections showed biliary hyperplasia and round cells, mast cells infiltration in the portal area beside hydropic degeneration in some hepatocytes **Figure 4**.

Figure 5. Effect of intraperitoneal administration of AuNRs 300µg/kg bwt 10 nm on liver and kidney of male albino rats on days-7 and 14 post treatments:

Liver: *On the 7th day post treatment,* the kuppfer cells appeared hypertrophied with mildly dilated sinusoids of some lobules Fig. 5 (A). A cloudy swelling, hydropic degeneration and some apoptotic changes occurred in few numbers of hepatocytes on day 14. Mild perivascular and round cell infiltrates were also observed. The kuppfer cells were mildly hypertrophied Fig.5 (B).

Kidney: A Mild to moderate congestion of renal blood vessels ,perivascular

Table 5: Effects of intraperitoneal injection of AuNRs 300 µg/ kg bwt 10nm on oxidant and anti-oxidant enzymes of male rats on Days-1, 3, 7 and 14 post treatments.

	1d		3d		7d		14d	
	Control	GNRs	Control	GNRs	Control	GNRs	Control	GNRs
CAT	1.71 ± 0.67	1.77 ± 0.41*	1.65 ± 0.13	1.46 ± 0.28	1.74 ± 0.26	1.71 ± 0.43	1.69 ± 0.43	1.69 ± 0.40
MDA	8.93 ± 0.10	11.29 ± 0.15	8.53 ± 0.20	18.35 ± 0.15	9.10 ± 0.04	9.10 ± 0.05	12.23 ± 0.16	8.81 ± 0.06
SOD	60.64 ± .35	51.38 ± 0.43	49.73 ± 0.30	71.38 ± 0.38	51.41 ± 0.46	50.73 ± 0.62	46.02 ± 0.38	48.0 ± 0.36
GPX	0.91 ± 0.02	0.79 ± 0.008	0.97 ± 0.02	0.51 ± 0.02	1.10 ± 0.02	1.09 ± 0.09	0.92 ± 0.03	1.58 ± 0.04

Table 6: Effects of intraperitoneal injection of AuNRs 30 µg/ kg bwt 10nm on oxidant and anti-oxidant enzymes of male albino rats on 60th day post injection.

	60d	
	Control	GNRs
CAT	2.37 ± 0.60	2.19 ± 0.70*
MDA	6.57 ± 0.22	13.87 ± 0.16*
SOD	30.18 ± 0.32	15.08 ± 0.38*
GPX	1.13 ± 0.03	0.68 ± 0.04*
Data represent means ± SE (n=6), * P<0.05 versus control		

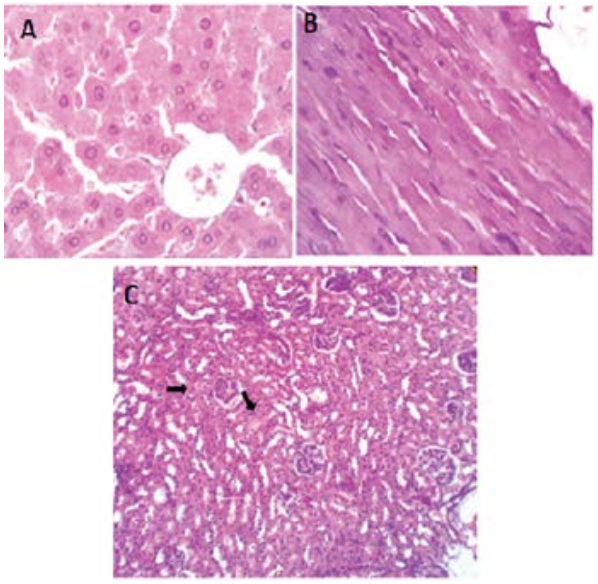

Figure 3: Liver and kidney tissues of control group: Photomicrograph of rat ' s Liver (A) & kidney (B) showing normal histo-morphological structures with preserved functional units and stromal frameworks. H&E X 200 and 400 (A&B). Photo-micrograph of rat ' s kidney tissue (C) showing normal histomorphological structures.(arrows).H&E X200.

edema , beside degenerative and necrotic changes in a mild to moderate number of renal tubular epithelium were seen. Mild interstitial edema and leucocytic infiltration, cystic dilatation of some renal tubules with flattened epithelial lining and hyaline casts in a few tubules were seen. The glomerular mesangial cells were hypertrophied in some glomeruli which appeared lobulated in a few cases on *day seven post treatment* Fig.5 C.

Fig. 5 D presented a Mild congestion of the renal blood vessels and capillaries, perivascular edema and interstitial leuckocytic infiltration, mostly lymphocytes. Degenerative changes in a mild to moderate number of cortical and medullary tubules (hydropic and fatty changes) with cystic dilatation in some of them could be detected. The glomerular mesangial cells were hypertrophied in a few glomeruli on *day fourteen post treatment* **(Figure 5)**.

Figure 6. Effect of intraperitoneal administration of AuNRs 30µg/kg bwt 10 nm on liver and kidney tissue of male albino rats on day 60 post treatments:

Liver: In most of the examined cases the hepatic parenchyma was apparently normal. A few hepatocytes showed irregular indistinct vacuoles or hydropic degeneration. The portal area in a few cases showed mild infiltrated of leukocytes, mostly round cells and the kupffer cells were mildly hypertrophied **Figure 6A**.

Kidney: Moderate number of renal tubules epithelium showed degenerative changes mainly hydropic degeneration and fatty change. A few glomeruli showed focal necrotic and apoptotic changes in the mesangial and endothelial cells as in **Figure 6B**.

Discussion

Gold nanoparticles have been popularized, because they have a unique properties including: high chemical stability, well-controlled size, and surface [15]. Furthermore, recent studies demonstrated that GNPs have potential antioxidant effects [16]. Despite that, oxidative stress remains a major challenge in the nanotoxicology field; however, one of the toxic mechanisms of nanoparticles is generation of reactive oxygen species (ROS) that has been widely studied [17].

The reason why intraperitoneal injection 300 µg/kg bwt GNRs caused a salient drop in serum SOD on day one post injection, comes from a fact that a sudden overproduction of O2 occurred, which in turn resulted in its decreased defensive ability and then returns to its normal functions gradually [18]. The same dose caused significant increase in serum CAT on the first day post injection, but declined on days three and seven post treatment in comparison

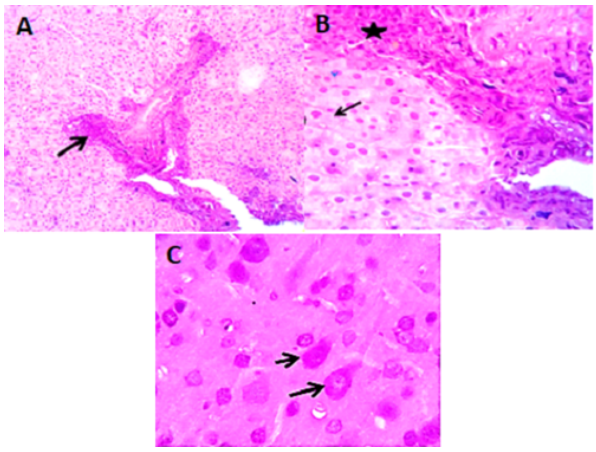

Figure 4: Photomicrograph of rat's liver (A&B) showing, biliary hyperplasia (arrow) and round cells, mast cells infiltration in the portal area (star) beside hydropic degeneration in some hepatocytes (arrow). H&E X 100(A), 400 (B). Photomicrograph of rat's kidney cystic renal tubules (C).

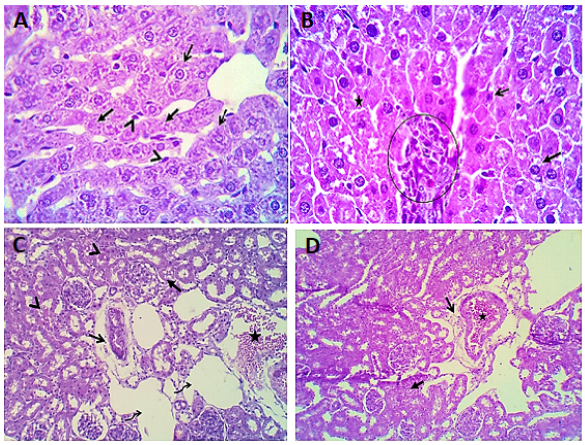

Figure 5: Photo-micrograph of rat's liver showing mild degenerative changes in some hepatocytes (cloudy swelling) (open arrows).The kupffer cells appears hypertrophied (arrow heads).H&E X 400 (A).Photo-micrograph of rats Liver showing cloudy swelling and hydropic degeneration (closed arrow) beside apoptotic changes in some hepatocytes (open arrow) associated with focal leuckocytic infiltration (round cells) in portal area (circle).H&E X 400 (B). Photo-micrograph of rat's kidney showing perivascular edema (open arrow), degenerative and necrotic changes of renal tubular epithelium (closed arrow), cystic dilatation with atrophied epithelium (curved arrow) and hyaline casts in a few tubules (arrow heads) with congestion of renal blood vessels (star). H&E X200 (C). Photo-micrograph of rat's kidney showing mild perivascular edema (open arrow), degenerative changes in some cortical tubules (closed arrow) and congestion of some renal blood vessels (star).H&E X 200 (D).

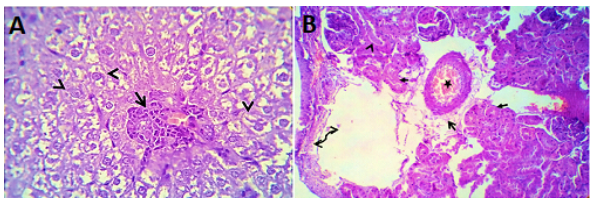

Figure 6: Photo-micrograph of rat's Liver showing hydropic degenerations in some hepatocytes (arrow heads). The portal area shows mild infiltration of leukocytes (round cells) (open arrow) (A).H&E X 400. Photo-micrograph of rat's kidney showing congestion of renal blood vessels, perivascular edema (star), renal tubules epithelium with degenerative and necrotic changes (closed arrows) and hyaline casts (arrow head) Focal sub capsular cyst is seen (double arrow) (B) H&E X 200.

with control rats. This result is correlated with the study published by Manke and his colleagues [19] who have reported that Nanoparticles-induced cellular/mitochondrial injury is proportional to physicochemical reactivity of AuNPs.

With regards to long term study, the intraperitoneal injection of 30 µg/kg bwt 10 nm caused significant decrease in serum CAT, SOD and GPX on the 60th day post injection. The same dose caused a significant increase in serum MDA on day 60 post treatment. It's known that the oxidant enzymes are ubiquitous. As previously pointed out, gold nanorods induced apoptotic and necrotic changes on various organs like liver and kidney tissues that resulted in alteration/fluctuation of oxidant and antioxidant enzymes levels. Apoptosis has been implicated as a major mechanism of cell death caused by NP-induced oxidative stress [20]. Amongst the different apoptotic pathways, the intrinsic mitochondrial apoptotic pathway plays a major role in metal oxide NP-induced cell death since mitochondria are one of the major target organelles for NP-induced oxidative stress [21].

Drug- induced liver diseases is still a major problem in drug development until these days, especially with a recent anti-cancer drugs like molecular targeted agents e.g. protein kinase inhibitors and check point inhibitor [22, 23]. The high dose and low dose of gold nanorods injected intraperitoneally induced significant alterations in serum value of liver enzymes on the first, the seventh and the fourteenth and sixtieth day post treatments. These data agreed with Abdelhalim, and Abdelmottaleb [24], who reported that administration of 10 nm gold nanoparticles caused significant rise in ALT and AST.

On the subject of the hepatic liver histopathological changes, it was previously

demonstrated that the liver sections of 300 µg/kg bwt GNRs treated rats showed kuppfer cells hypertrophy on the third day post injection and this hypertrophy begin to increase along the entire period of the study associated with cloudy swelling, apoptotic and degenerative changes. This swelling occurred by the following: 1) GNPs caused massive Na/H2O influx that resulted in membrane dysfunction 2) leakage of lysosomal hydrolytic enzymes that cause cytoplasmic degeneration and macromolecular crowding [25].

On the 60th post injection, the liver parenchyma appeared normal with a mild leucocyte infiltration; this may indicate that the gold nanorods have been cleared from the body as revealed by Cai and his team [26] who reported the hepatic uptake and location of AuNRs using transmission electron microscope resulted in removal of AuNRs from blood circulation by Kupffer cells.

As to kidney function parameters and histopathology, urea and creatinine values of AuNRs 300µg/kg bwt i.p and AuNRs 30µg/kg bwt treated rats increased in a significant manner corresponding to control group. These data were in agreement with Wang and his colleagues [27] who injected 1 mg/ kg bwt AuNRs to male albino rats via intravenous route and the result was increase in serum urea and creatinine as well. Another elucidation, PEG-coated gold nanorods are cationic particles that have higher accumulation within the kidneys than the neutral on [28]. Our results agreed with chou and his team [29], because they explained that the PEG coated AuNRs with 13 nm in size can accumulate for 7 days. Some theories reported that when gold nanorods exceed 6 nm, it cannot easily be eliminated by the kidneys, so they remain in circulation for a longer time. On day 60 post injection, the kidney histopathological section revealed some apoptotic changes and renal blood vessel congestion. This is contributed to the remaining of AuNRs in circulation for long time as mentioned by Yu and Zheng [30].

Conclusion

From this study, it has been concluded that gold nanorods adversely affected hepato-renal biochemical parameters. Also, Gold nanorods induced marked degenerative and necrotic changes in histomorphological architecture of liver and kidney tissues. Moreover, it was evident that gold nanorods exhibited significant alterations in oxidant and anti-oxidant enzymes. Thus, further molecular toxicodynamic studies are needed to be performed.

References

1. Peer Dan, Jeffrey M Karp, Seungpyo Hong, Omid C Farokhzad and Robert Langer et al. "Nano carriers as an Emerging Platform for Cancer Therapy." *Nat Nanotechnol* 2(2020):751-760.
2. Astruc Didier."Introduction to nanomedicine."*Molecules* 21(2016):4.
3. Rosenblum Daniel, Nitin Joshi, Wei Tao, Jeffrey M Karp and Dan Peer. "Progress and challenges towards targeted delivery of cancer therapeutics." *Nat Commun* 9(2018):1-12.
4. Tiwari Pooja Munnilal, Erdal Eroglu, Swapnil Subhash Bawage, Komal Vig and Michael E. Miller et al. "Enhanced intracellular translocation and biodistribution of gold nanoparticles functionalized with a cell-penetrating peptide (VG-21) from vesicular stomatitis virus." *Biomaterials* 35(2014):9484-9494.
5. Riley Rachel S and Emily S Day."Gold nanoparticle-mediated photothermal therapy: applications and opportunities for multimodal cancer treatment." *Wiley Interdiscip Rev Nanomed Nano Biotechnol* 9(2017): e1449.
6. Nikoobakht Babak and Mostafa A El-Sayed. "Preparation and growth mechanism of gold nanorods (NRs) using seed-mediated growth method." *Chem Mater* 15(2003):1957-1962.
7. Zhang Xiao-Dong, Hong-Ying Wu, Yue-Ying Wang Di Wu, Jian-Hui Chang and Zhi-Bin Zhai et al. "Toxicologic effects of gold nanoparticles in vivo by different administration routes." *Int J Nanomedicine* 5(2010):771.
8. Lankveld Daniëlle PK, Raja G Rayavarapu, Petra Krystek, Agnes G Oomen and Hennie W Verharen et al."Blood clearance and tissue distribution of PEGylated and non-PEGylated gold nanorods after intravenous administration in rats." *Nanomedicine* 6(2011):339-349.
9. Beyer Jr Wayne F and Irwin Fridovich."Assaying for superoxide dismutase activity: some large consequences of minor changes in conditions." *Anal Biochem* 161(1987):559-566.
10. Paglia Donald E and William N Valentine."Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase." *J Clin Med* 70(1967):158-169.
11. Aebi H. "Catalase in vitro Methods Enzymol 105: 121–126."(1984).
12. Utley Henry G, Frederick Bernheim and Paul Hochstein. "Effect of sulfhydryl reagents on peroxidation in microsomes."*Arch Biochem Biophys* 118(1967):29-32.
13. McDonald, John H *Handbook of biological statistics*. Sparky House Publishing, Baltimore,(2009).
14. Suvarna Kim S, Christopher Layton and John D Bancroft. *Bancroft's theory and practice of histological techniques*. Elsevier Health Sciences,(2018).
15. Nicol James R, Dorian Dixon and Jonathan A Coulter. "Gold nanoparticle surface functionalization: a necessary requirement in the development of novel nanotherapeutics." *Nano Med* 10(2015):1315-1326.
16. Nicol James R. "Gold nanoparticle surface functionalization: a necessary requirement in the development of novel nanotherapeutics." *Nanomedicine* 10(2015):1315-1326.
17. Barath Mani Kanth Selvaraj, Kalimuthu Kalishwaralal, Muthuirulappan Sriram, Suresh Babu Ram Kumar Pandian and Hyung-seop Youn et al. "Anti-oxidant effect of gold nanoparticles restrains hyperglycemic conditions in diabetic mice." *J. Nano Biotechnol* 8(2010):1-15.
18. Pan Yu, Annika Leifert, David Ruau, Sabine Neuss and Jörg Bornemann et al. "Gold nanoparticles of diameter 1.4 nm trigger necrosis by oxidative stress and mitochondrial damage." *Small* 5(2009):2067-2076.
19. Wan Yujie, Junli Li, Hongxuan Ren, Jin Huang and Hong Yuan. "Physiological investigation of gold nanorods toward watermelon." *J Nanosci Nanotechnol* 14(2014):6089-6094.
20. Manke Amruta, Liying Wang and Yon Rojanasakul. "Mechanisms of nanoparticle-induced oxidative stress and toxicity." *Biomed Res Int* (2013).
21. Eom Hyun-Jeong and Jinhee Choi."p38 MAPK activation, DNA damage, cell cycle arrest and apoptosis as mechanisms of toxicity of silver nanoparticles in Jurkat T cells." *Environ Sci Technol* 44(2010):8337-8342.
22. Ma Dan-Dan and Wan-Xi Yang. "Engineered nanoparticles induce cell apoptosis: potential for cancer therapy."*Oncotarget* 7(2016):40882.
23. Mitra Vikramjit and Jane Metcalf. "Metabolic functions of the liver." *Anaesth Intensive Care Med* 10(2009): 334-335.
24. Abdelhalim Mohamed Anwar K and Sherif A Abdelmottaleb Moussa. "The gold nanoparticle size and exposure duration effect on the liver and kidney function of rats: *In vivo*." *Saudi J Biol Sci* 20(2013):177-181.
25. Sun Hainan, Jianbo Jia, Cuijuan Jiang and Shumei Zhai. "Gold nanoparticle-induced cell death and potential applications in nanomedicine." *Int J Mol Sci* 19(2018):754.
26. Cai Huatang, Yuhui Ma, Ziran Wu, Yayun Ding and Peng Zhang, et al."Protein corona influences liver accumulation and hepatotoxicity of gold nanorods." *NanoImpact* 3(2016):40-46.
27. Wang Jing, Ru Bai, Ru Yang, Jing Liu and Jinglong Tang, et al. "Size-and surface chemistry-dependent pharmacokinetics and tumor accumulation of engineered gold nanoparticles after intravenous administration." *Metallomics* 7(2015):516-524.

28. Lipka Jens, Manuela Semmler-Behnke, Ralph A Sperling, Alexander Wenk and Shinji Takenaka et al. "Biodistribution of PEG-modified gold nanoparticles following intratracheal instillation and intravenous injection." *Biomaterials* 31(2010):6574-6581.

29. Cho Wan-Seob, Minjung Cho, Jinyoung Jeong, Mina Choi and Hea-Young Cho et al. "Acute toxicity and pharmacokinetics of 13 nm-sized PEG-coated gold nanoparticles." *Toxicol Appl Pharmacol* 236(2009): 16-24.

30. Yu Mengxiao and Jie Zheng. "Clearance pathways and tumor targeting of imaging nanoparticles." *ACS Nano* 9(2015):6655-6674.

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