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Oral Exposure to Silver/Gold Nanoparticles: Status of Rat Lipid Profile, Serum Metabolites and Tissue Morphology

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Study investigated the effect of oral administration of gold-silver nanoparticles on rat biochemical parameters and tissue morphology. Wistar rats weighing approximately 180±7 g were randomly assigned into four groups. Animals in the control group received distilled water once daily for 30 days while, those in the treatment groups were administered 10, 50 and 100 mg kg^{-1} b.wt. gold-silver nanoparticles. The rats were sacrificed under slight anesthesia, 24 h after the last treatments. Blood and vital organs including the heart, kidney and liver were collected and prepared for biochemical and histopathological determinations. Exposure to Ag/Au nanoparticles altered the rat serum lipid profile; lowering the HDL-C while raising the atherogenic index. Exposure of Ag/Au nanoparticles in rats caused significant alteration to the levels of serum albumin, total protein, bilirubin, urea and creatinine. The activities of alanine transaminase, aspartate transaminase and alkaline phosphatase in rat serum and tissues were also significantly altered by Ag/Au nanoparticles exposure. The histopathological examination revealed inflammation and cellular degeneration caused by exposure to the Ag/Au nanoparticles. We show evidence that Ag/Au nanoparticles elevated atherogenic index, as well as caused biochemical and morphological alterations, reminiscent of cellular injury.

Key words: Metal nanoparticles, safety evaluation, lipid profile

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INTRODUCTION

Metal nanoparticles, especially silver and gold, have been implicated for several bioactivities (Lee *et al.*, 2002; Saha *et al*., 2008; Barathmanikanth *et al*., 2010; Salma *et al*., 2011). The antimicrobial property of silver nanoparticles has led to their wide-spread use in bedding, water purification, tooth paste, shampoo, rinse, infant nipples nursing bottles, fabrics, deodorants, filters, kitchen utensils, toys and humidifiers (Maynard *et al*., 2006). Gold nanoparticles are compatible for a wide range of biological applications, because of their unique physical and chemical properties. Recently, the applications of gold nanoparticles have expanded into various biomedical fields (biosensors, immunoassays, genomics, photo thermolysis of cancer cells, microorganisms detection and control, targeted drug delivery, optical imaging, monitoring of biological cells and tissues by exploiting resonance scattering, or *in vivo* photo acoustic techniques (Gupta *et al.*, 2007; Adeyemi and Sulaiman, 2015). Despite the wide application of nanoparticles, there is a serious lack of information concerning their impact on human health and the environment. Very little is known about the toxicity of nano-sized particles, however, the size and surface area are recognized as important determinants for toxicity (Ji *et al*., 2007). The increasing usage of these nanoparticles and nanomaterials, underscores research efforts to identify probable or likely toxic events that may ensue following exposure.

The present study evaluated the effect of the oral exposure of Ag/Au nanoparticles on biochemical indices and tissue morphology in rats.

MATERIALS AND METHODS

Nanoparticles: The silver/gold nanoparticles (Ag/Au nanoparticles) were from the Nanomedicine and Biomedical Target Laboratory, Department of Biochemistry, Microbiology and Biotechnology, Rhodes University, South Africa. The preparation procedures and characterization have been previously reported (Adeyemi and Whiteley, 2013, 2014). The dark brown Ag/Au nanoparticles absorbed maximally at 420 and 550 nm for Ag and Au respectively. The diameter size of the nanoparticles ranges between 10-40 nm.

Experimental animals: Male Wistar rats of average weight of 180+7 g were obtained from the animal unit of the Department of Biochemistry, University of Ilorin, Nigeria.

Chemicals and reagents: The assay kits for Total Cholesterol (TC), triacylglycerol (TAG), High Density Lipoprotein (HDL-C), Free Glycerol (FG), creatinine (CREA), urea, bilirubin (BIL), albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were products of Randox Laboratory Limited, Atrim, United Kingdom. All other reagents and chemicals used were of analytical grade and supplied by Sigma Aldrich Inc., St. Louis, USA.

Animal groupings and treatments: The animals were kept in plastic cages contained in the experimental animal house and allowed to acclimatize for two weeks before commencement of treatments. Animals were maintained under standard hygienic conditions with alternate 12 h light and dark cycle. Animals were given free access to rat chow and clean water *ad libitum*. Handling of animals was consistent with relevant guidelines on the care and use of laboratory animals (National Research Council, 2011). The details of animal groupings are as shown below:

Group 1: Served as the Control and received 0.5 mL of distilled water
Group 2: Received 0.5 mL of 10 mg kg^{-1} b.wt. of Ag/Au nanoparticles
Group 3: Received 0.5 mL of 50 mg kg^{-1} b.wt. of Ag/Au nanoparticles
Group 4: Received 0.5 mL of 100 mg kg^{-1} b.wt. of Ag/Au nanoparticles

The treatments were orally administered by means of a gavage. Treatments were daily and lasted for 30 days.

Preparation of serum and tissue homogenates: The animals were sacrificed under ethyl ether anesthesia 24 h after cessation of treatments. The blood was collected into a clean and sterile sample bottles. The blood was centrifuged at 3000 g for 10 min using a Uniscope Laboratory Centrifuge (Model SM800B) to yield the serum, which was stored frozen until required for analyses. The vital organs including the liver, kidney and heart were removed, blotted, weighed and homogenized in ice-cold 0.25 M sucrose solution (1:5 w/v). The homogenates were kept frozen until used for the biochemical analyses. Part of each excised tissue was fixed in 10% Buffered Neutral Formalin (BNF) and used for the histopathological examination.

Determination of biochemical parameters: All biochemical measurements were done using Spectronic 21 spectrophotometer (Bausch and Lomb, NY). The activities of aspartate transaminase (AST) (E.C. 2.6.1.1), alanine transaminase (ALT) (E.C. 2.6.1.2), alkaline phosphatase (ALP) (E.C.3.1.3.1), albumin (ALB), bilirubin (BIL), creatinine, urea, serum total cholesterol

concentration (TC), High Density Lipoprotein Cholesterol (HDL-C) and triacylglycerol (TAG) was assayed using the Randox assay kits (Crumlin, UK). The concentration of serum Low Density Lipoprotein (LDL-C) was estimated using Friedewald formula (Warnick *et al*., 1990) while, the Atherogenic Index (AI) was estimated by finding the ratio of the TC to HDL-C concentration. The protein content of the serum and homogenates was determined using the Biuret method as previously described by Sulaiman and Adeyemi (2010).

Histological examination: The preparation of tissue sections for histological examination under light microscope followed the standard embedding and H-E staining protocol. The photomicrographs were captured at 100X using the software, *Presto! Image Folio package*.

Statistical analysis: Data was analyzed using the analysis of variance (ANOVA) and Duncan multiple range test on SPSS package. The data were presented as Mean±Standard error of mean. Group mean value at 5% level of confidence ($p<0.05$) was considered significant.

RESULTS

Average weight of animals: Figure 1 shows the average rat weight after exposure to silver/gold nanoparticles. At the highest dosage, the nanoparticles caused reduction ($p<0.05$) in rat weights relative to control. The rat organ weights were also decreased by nanoparticle treatment when compared to the control (Table 1). In like manner, the percentage liver and kidney-to-body weight ratio of rats administered with Ag/Au nanoparticle for 30 days decreased relative to the control (Table 2).

Lipid profile: The nanoparticles altered the rat lipid profile following daily exposure for 30 days (Table 3 and 4). The estimation of LDL in rat serum following daily exposure to Ag/Au nanoparticle reveals significant elevation at the dose of 10 mg kg^{-1} b.wt. compared with the control. The atherogenic index was also estimated for rats after exposure to Ag/Au nanoparticles for 30 days. Data show elevation in atherogenic index caused by Ag/Au nanoparticles at the highest dose.

Total protein: The rat serum total protein concentration was reduced following daily exposure to Ag/Au nanoparticles. In contrast, levels of total protein rat heart, liver and kidney tissues were significantly elevated relative to the control (Table 5).

Table 1: Weight of rat organs following oral exposure to silver/gold nanoparticles

	Organs weight of rats (g)		
Groups	Heart	Liver	Kidney
Control	1.40±0.00	8.13±0.09	2.10±0.12
Ag/Au 10 (mg kg^{-1})	1.43±0.03	7.60±0.58*	1.90±0.10*
Ag/Au 50 (mg kg^{-1})	1.33±0.12	7.73±0.58*	1.90±0.10*
Ag/Au 100 (mg kg^{-1})	1.40±0.00	7.47±0.32*	1.83±0.15*

Values are expressed as Mean±SEM (n = 3), *Significant relative to control at $p<0.05$, Ag/Au: Silver/gold

Table 2: Organ-to-body weight ratios of rat orally administered with silver/gold nanoparticles

	Percentage organ/body weight ratios (g)		
Groups	Heart	Liver	Kidney
Control	0.82±0.04	4.76±0.26	1.23±0.12
Ag/Au 10 (mg kg^{-1})	0.77±0.06	4.10±0.45*	1.02±0.05*
Ag/Au 50 (mg kg^{-1})	0.78±0.08	4.58±0.55*	1.12±0.14*
Ag/Au 100 (mg kg^{-1})	0.87±0.04*	4.66±0.09*	1.13±0.03*

Values are expressed as Mean±SEM (n = 3), *Significant relative to control at $p<0.05$, Ag/Au: Silver/gold

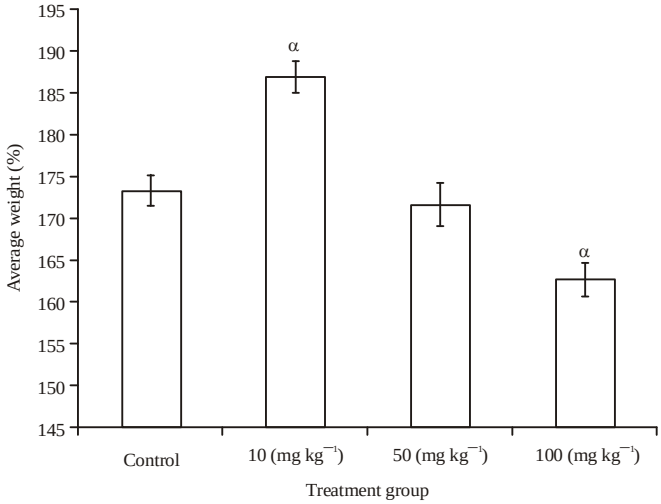

Fig. 1: Average weight of rat following oral exposure to silver/gold nanoparticles at different dosages. Data is expressed as Mean±SEM (n = 3). α is significant at $p<0.05$ relative to the control

Serum metabolites: For the evaluation of Ag/Au nanoparticles on the renal and liver function indices, serum urea, creatinine, albumin and bilirubin concentrations were determined. The rat serum total bilirubin level was raised ($p<0.05$), consequent upon the administration of Ag/Au nanoparticles (Table 6). In contrast, the levels of rat serum urea, albumin and creatinine were significantly reduced by exposure to Ag/Au nanoparticles relative to the control.

Table 3: Effect of silver/gold nanoparticles on the level of rat serum total cholesterol, triacylglyceride and free glycerol

Groups	Total cholesterol (mmol L^{-1})	Triacylglyceride (mmol L^{-1})	Glycerol (mmol L^{-1})
Control	0.26±0.05	0.41±0.30	0.30±0.30
Ag/Au 10 (mg kg^{-1})	0.30±0.00*	0.82±0.59*	0.91±0.37*
Ag/Au 50 (mg kg^{-1})	0.19±0.05*	0.31±0.20*	0.20±0.20*
Ag/Au 100 (mg kg^{-1})	0.58±0.11*	0.30±0.04*	0.19±0.04*

Values are expressed as Mean±SEM (n = 3), *Significant relative to control at $p<0.05$, Ag/Au: Silver/gold

Table 4: Effect of silver/gold nanoparticles on the level of rat serum high density lipoprotein, low density lipoprotein and atherogenic index

Groups	HDL-C (mmol L^{-1})	LDL-C (mmol L^{-1})	Atherogenic index
Control	0.50±0.71	0.08±0.03	1.12±0.18
Ag 10 (mg kg^{-1})	0.46±0.01	0.20±0.04*	0.34±0.01*
Ag 50 (mg kg^{-1})	0.62±0.11*	0.07±0.02	0.47±0.05*
Ag 100 (mg kg^{-1})	0.24±0.05*	0.06±0.00	5.52±0.09*

Values are expressed as Mean±SEM (n = 3), *Significant relative to control at $p<0.05$, Ag/Au: Silver/gold, HDL: High density lipoprotein, LDL: Low density lipoprotein

Other biochemical indices: In order to further evaluate the effect of the administration of Ag/Au nanoparticle on vital organ functions, activities of AST, ALT and ALP were determined in rat serum and tissues. Ag/Au nanoparticle exposure in rats led to significant decreases in the activities of serum and tissue AST, when compared with the control (Table 7). The effect on the activities of ALT and ALP are as presented in Table 8 and 9.

Histopathological examination: Histological examination of rat heart following Ag/Au nanoparticle administration revealed mild degeneration of cardiac tissue and inflammation (Fig. 2). The control group

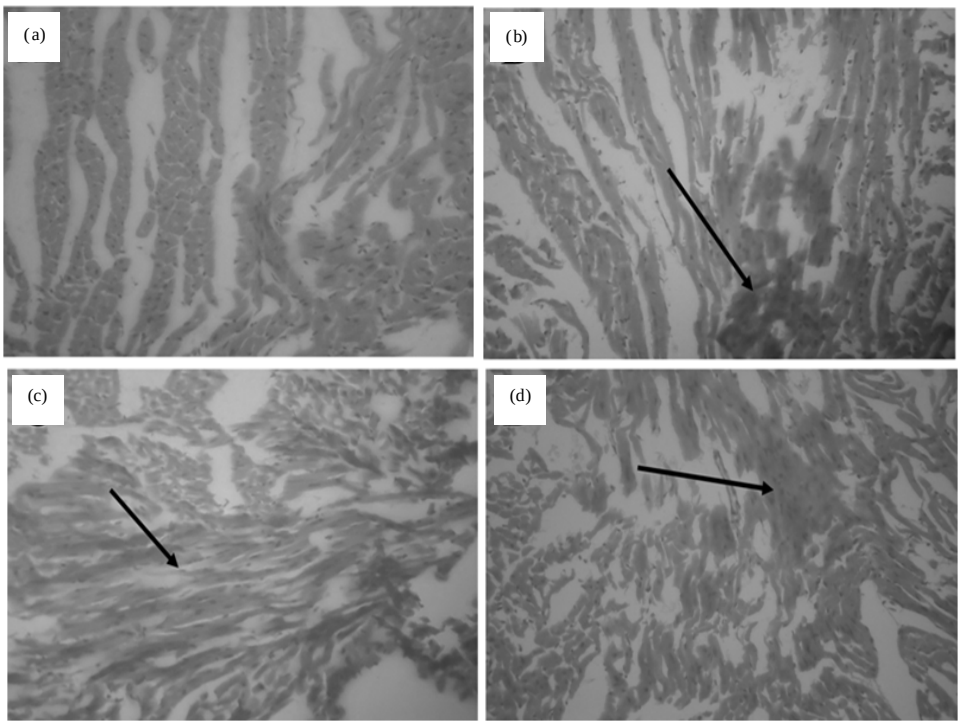

Fig. 2(a-d): Photomicrographs of rat heart following sub-chronic exposure to silver/gold nanoparticles at different dosages, (a) Control group given distilled water showing intact cellular morphology, (b) Group given silver/gold nanoparticles at 10 mg kg^{-1}, (c) Group given silver/gold nanoparticles at 50 mg kg^{-1} and (d) Group given silver/gold nanoparticles at 100 mg kg^{-1} body weight showing inflammation and cellular degeneration. H and E staining (×400)

Table 5: Effect of silver/gold nanoparticles on the level of rat serum and tissue total protein

	Total protein concentration (g dL^{-1})			
Group	Serum	Heart	Kidney	Liver
Control	2.52±0.51	3.75±1.47	6.65±1.94	7.72±2.34
Ag/Au 10 (mg kg^{-1})	2.84±0.30	12.81±4.46*	3.03±1.13*	9.88±4.92
Ag/Au 50 (mg kg^{-1})	2.01±1.65*	7.82±5.04*	10.95±3.50	15.85±8.78*
Ag/Au 100 (mg kg^{-1})	2.35±0.97*	9.37±0.66*	9.95±3.90	8.54±4.90

Values are expressed as Mean±SEM (n = 3), *Significant relative to control at p<0.05, Ag/Au: Silver/gold

Table 6: Effect of silver/gold nanoparticles on the level of rat serum metabolites

Groups	Albumin (g dL^{-1})	Bilirubin (mmol L^{-1})	Creatinine (µmol L^{-1})	Urea (mmol L^{-1})
Control	2.21±0.25	2.59±0.32	17.85±1.71	41.44±0.00
Ag/Au 10 (mg kg^{-1})	1.57±0.13*	19.79±0.00*	15.95±1.06*	35.78±4.57*
Ag/Au 50 (mg kg^{-1})	0.21±0.04*	12.95±1.06*	15.21±0.37*	22.48±7.50*
Ag/Au 100 (mg kg^{-1})	1.93±0.17*	8.94±0.163*	17.48±1.43*	30.85±4.57*

Values are expressed as Mean±SEM (n = 3), *Significant relative to control at p<0.05, Ag/Au: Silver/gold

Table 7: Effect of silver/gold nanoparticles on the activity of rat serum and tissue aspartate transaminase

	AST (U L^{-1})			
Groups	Serum	Liver	Kidney	Heart
Control	51.67±5.78	57.17±4.44	54.67±3.24	51.83±9.49
Ag/Au 10 (mg kg^{-1})	34.83±23.35*	18.17±8.57*	16.33±2.83*	20.50±10.26*
Ag/Au 50 (mg kg^{-1})	23.83±7.78*	31.67±7.10*	20.00±4.62*	23.00±9.88*
Ag/Au 100 (mg kg^{-1})	29.67±3.94*	33.17±7.16*	23.83±5.17*	31.83±4.15*

Values are expressed as Mean±SEM (n = 3). * Significant relative to control at p<0.05, Ag/Au: Silver/gold, AST: Aspartate amino transferase

Table 8: Effect of silver/gold nanoparticles administration on the activity of rat serum and tissue alanine transaminase

	ALT (U L^{-1})			
Groups	Serum	Liver	Kidney	Heart
Control	53.0±2.52	26.7±1.20	87.3±3.84	17.7±1.45
Ag/Au 10 (mg kg^{-1})	70.7±5.78*	41.0±1.53*	79.7±3.53*	74.7±10.5*
Ag/Au 50 (mg kg^{-1})	61.7±5.49*	75.3±5.33*	63.0±4.73*	68.0±3.61*
Ag/Au 100 (mg kg^{-1})	36.300±0.88*	38.300±3.33*	51.700±4.05*	47.000±3.00*

Values are expressed as Mean±SEM (n = 3). *Significant relative to control at p<0.05, Ag/Au: Silver/gold, ALT: Alanine amino transaminase

Table 9: Effect of silver/gold nanoparticles on the activity of rat serum and tissue alkaline phosphatase

	ALP (U L^{-1})			
Groups	Serum	Liver	Kidney	Heart
Control	463.96±74.21	427.05±69.74	491.28±26.61	177.50±38.95
Ag/Au 10 (mg kg^{-1})	182.80±12.43*	156.27±1.50*	175.78±21.09*	159.07±32.90*
Ag/Au 50 (mg kg^{-1})	127.24±16.17*	182.02±37.69*	92.50±27.22*	274.77±78.18*
Ag/Au 100 (mg kg^{-1})	174.37±21.88*	168.80±23.64*	220.49±41.80*	191.82±23.11*

Values are expressed as Mean±SEM (n = 3), *Significant relative to control at p<0.05, Ag/Au: Silver/gold, ALP: Alkaline phosphatase

showed no incidence of cellular alteration in the cardiac tissue. The examination of rat renal sections for morphological changes revealed mild inflammation caused by the administration of Ag/Au nanoparticle (Fig. 3). The control group showed intact cellular architecture. Furthermore, exposure to Ag/Au nanoparticle caused cellular lesion in rat hepatic tissue. The cellular alteration caused by the nanoparticle administration includes inflammation and cellular cracking (Fig. 4). The control group showed no visible alteration to cellular architecture of the hepatic tissue.

DISCUSSION

The increasing usage of nanoparticles especially Ag and Au nanoparticles for biomedical purposes necessitates the safety evaluation of these nanoparticles. Recent findings have shown that nanoparticles, because of their small sizes, behave differently from the parent material and have potential to predispose to oxidative cellular damage (Hudecova *et al*., 2012; Adeyemi and Faniyan, 2014).

The daily administration of Ag/Au nanoparticles at the highest dose (100 mg kg^{-1}) to rats for 30 days caused significant reductions to the average weights relative to the control. This may be an early symptom of ensuing toxic events caused by the nanoparticle exposure. Previous studies have associated changes to body weight with toxicity of drugs or chemicals (Orisakwe *et al*., 2004; Adeyemi and Sulaiman, 2014).

In the present study, exposure of rats to Ag/Au nanoparticles caused inconsistent alterations to the levels

of TC, TAG, FG as well as HDL-C. The imbalances in the lipid profile status of cells could predispose to several health consequences. When the level of TC, TAG and LDL are high, it could raise the risk of cardiovascular disorder. A reduction in the HDL-C could be hazardous. The HDLs may actually serve to retard or reduce atherosclerotic buildup (Olukanni *et al.*, 2013). The administration of nanoparticles decreased the HDL-C in the serum at the highest dose. This may increase the risk of cardiovascular diseases. More so, the AI was elevated by nanoparticle administration at the highest dose. The rise in the atherogenic index may predispose to the development of atherosclerosis (Adeyemi and Akanji, 2011a; Olukanni *et al*., 2013).

Total protein is composed of albumin and globulin and reflects the balance of protein biosynthesis and catabolism. The significant decrease in total protein at the dose of 100 mg kg^{-1} might be due to decreased synthesis, increased loss, increased catabolism, malabsorption or liver disease consequent upon the administration of the nanoparticles (Guyton and Hall, 2000). The level of serum albumin could be used to evaluate the synthetic function of the liver. Decrease in albumin has been observed in serum of patients with tissue inflammation and damages (Gabay and Kushner, 1999), which suggest that the tissues of the experimental rats might have been injured following administration of the nanoparticles.

The level of rat serum bilirubin increased following the administration of Ag/Au nanoparticles. Previous study has attributed demonstrated that increased red blood cell hemolysis could cause elevated bilirubin beyond the hepatic function capacity (Adeyemi *et al.*, 2012).

Furthermore, to evaluate effect of the nanoparticle exposure on kidney function, the serum urea and creatinine levels were determined. Serum urea and creatinine are useful indices for evaluating the status of renal functions (Gross *et al*., 2005). A rise in the level of serum urea may imply impaired renal excretion (Adeyemi and Akanji, 2012). However, in the present study, serum urea decreased. The decrease in the concentration of serum urea after the administration of the nanoparticles might be attributable to decreased amino acid degradation by the liver. This is more plausible considering the fact that the nanoparticle exposure also caused decreased level of rat serum albumin. The level of serum albumin has been associated with the synthetic

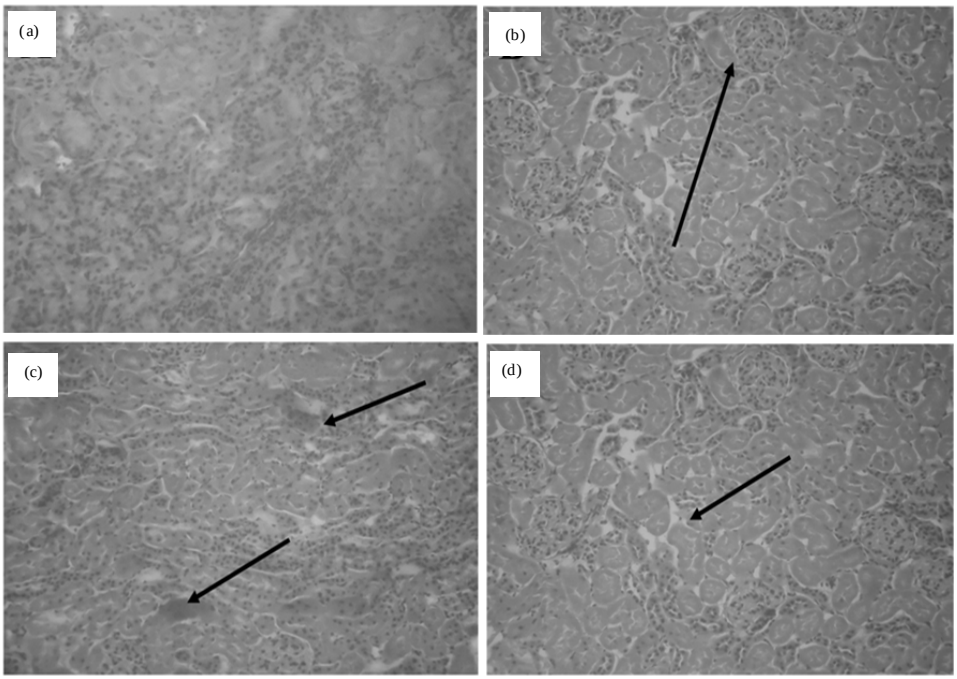

Fig. 3(a-d): Photomicrographs of rat kidney following sub-chronic exposure to silver/gold nanoparticles at different dosages, (a) Control group given distilled water showing intact cellular morphology, (b) Group given silver/gold nanoparticles at 10 mg kg^{-1} body weight showing mild inflammation, (c) Group given silver/gold nanoparticles at 50 mg kg^{-1} body weight and (d) Group given silver/gold nanoparticles at 100 mg kg^{-1} body weight showing inflammation and cellular degeneration. H and E staining (×400)

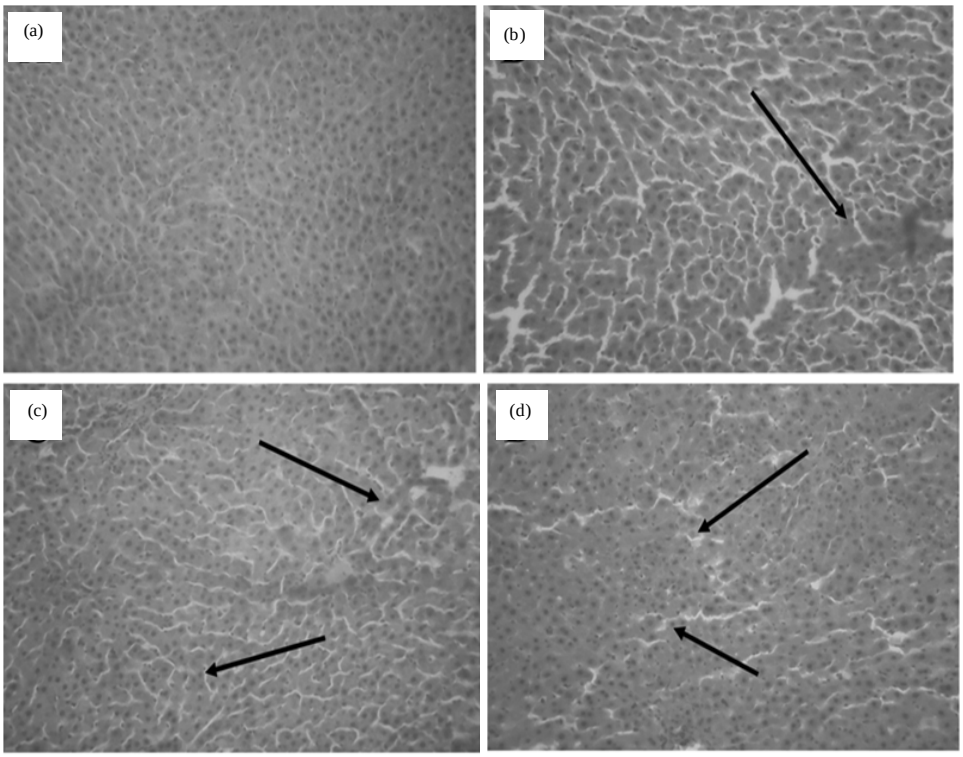

Fig. 4(a-d): Photomicrographs of rat liver following sub-chronic exposure to silver/gold nanoparticles at different dosages, (a) Control group given distilled water showing intact cellular morphology, (b) Group given silver/gold nanoparticles at 10 mg kg^{-1} body, (c) Group given silver/gold nanoparticles at 50 mg kg^{-1} and (d) Group given silver/gold nanoparticles at 100 mg kg^{-1} body weight showing inflammation and cellular degeneration. H and E staining (×400)

function of the liver (Adeyemi *et al.*, 2010, 2012). In the present study, the level of rat serum creatinine was reduced significantly and may suggest enhanced glomerular clearance or impaired muscle metabolism.

The measurement of the activity of some enzymes could be used to evaluate for cellular toxicity arising from exposure to chemical compounds including drugs (Adeyemi and Akanji, 2011b). The alanine and aspartate aminotransferases (ALT and AST) are 'markers' of liver damage and can thus be used to assess liver cytolysis (Adeyemi and Sulaiman, 2014; Sulaiman and Ekanem, 2009). The administration of Ag/Au nanoparticles decreased the activities of AST and ALT in rat serum, liver, kidney and heart relative to the control. This may be due to inactivation of the enzyme molecules by the nanoparticles or their metabolites. Recent findings have demonstrated the potential of Ag or Au nanoparticles to alter protein structure by forming a complex with the thiol (-SH) group within the protein molecule (Adeyemi and Whiteley, 2013, 2014). The Ag or Au nanoparticles have affinity for -SH groups and as such could interfere with the functional state of a protein molecule by binding to the thiol groups. On the other hand, the activity of rat ALT increased in the serum, liver and heart. The elevation of ALT level in rat serum and tissues may be the result of adaptive mechanism by the animals in order to offset the stress imposed by the nanoparticle administration. Living cells have been reported to increase the *de novo* synthesis of proteins in response to stressors such as drugs or chemical agents (Adeyemi and Sulaiman, 2012). The elevation of ALT activity may also be an early indicator for hepatotoxicity consequent upon exposure to nanoparticles. Elevated level of serum ALT has been linked with hepatic injury (Adeyemi and Akanji, 2012; Sulaiman *et al.*, 2014). A previous report has revealed that metal nanoparticles altered the biochemical parameters causing cellular damage (Kim *et al*., 2009). The present findings on ALT and AST activities following exposure to nanoparticles are consistent with an earlier report (Salma *et al.*, 2011), which demonstrated that metal nanoparticles have potential to alter the activity of transaminases.

Histological examination of tissue sections could serve as complementary evidence to the biochemical

evaluation. The incidence of inflammation, cellular degeneration and hyperchromic anemia, which characterized the nanoparticle-treated tissues may suggest likely cellular toxicity. The cellular lesions caused by the nanoparticle administration were absent in the control group. The morphological alterations are evidence that support further the potential of the nanoparticles to cause cellular damage. Earlier report by Maneewattanapinyo *et al*. (2011) showed the LD_{50} of Ag nanoparticles to be >5000 mg kg^{-1}, however, the present data suggest caution in exposure, essentially because a separate study has demonstrated that nanoparticles could sequester and bio-accumulate in tissues (Yang *et al*., 2008).

There is increasing usage of nanoparticles for biomedical purposes. However, our knowledge and understanding of the effect of these nanoparticles on living cells or biochemical indices remain insufficient (Adeyemi *et al*., 2014). It has therefore, become imperative that studies which aim to determine the biochemical evaluations of nanoparticles, be encouraged. To our knowledge, this is the first report showing evidence that nanoparticles altered lipid profile and elevated the atherogenic index.

CONCLUSION

The present data reveal the status of some cellular biochemistry and morphological indices in the presence of Ag/Au nanoparticles and would contribute to aid our understanding of the potential effect of the exposure of nanoparticles on cellular system.

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