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Toxicological Assessment of Silver Nanoparticles and Colchicine on Biochemical Indices in Albino Wistar Rats

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Abstract

Silver nanoparticles (AgNPs) have numerous biomedical uses due to its excellent biocompatibility, antibacterial activity, antiviral, antifungal and anti-inflammatory activity. The present research was carried out with the aim to determine effect of silver nanoparticles (AgNps) and colchicine on albino wistar rats. The silver nanoparticle was administered at the dosages of 1.11, 1.48, 1.85 and 2.22 mg/kg rat body weight to groups B to E respectively. Group A, which serve as the positive control group was administered with distilled water while group F was treated with a reference drug, called colchicine. The rats were sacrificed under slight anaesthesia twenty-four (24) hours after the last treatment and the effect of

the silver nanoparticles and the colchicine on different enzymes and substrates in serum and selected organs were studied. Administration of silver nanoparticle has no significant differences ($p > 0.05$) on the average body weight, weight of organs and organ-body weight ratios of test rats when compared with the positive control rats. Administration of the silver nanoparticles to the test groups causes a significant alteration ($p < 0.05$) on the activities of alanine transferase, aspartate transferase, alkaline phosphatase and concentrations of total protein, albumin, urea and creatinine compared with the positive control group. The results obtained suggested that the effects of silver nanoparticles on hepatocytes at high doses (1.85mg/kg and 2.22mg/kg) led to the disruption and leakage of its enzymes into the blood stream. High concentrations of alkaline phosphatase (ALP), Alanine transaminase (ALT) and Aspartate transaminase (AST) were found the serum of the rats, indicating liver damage. We therefore recommend that the usage of silver nanoparticles as drug carrier should be at low doses to prevent hepatotoxicity and other related health issues.

Keywords: Silver nanoparticles, Colchicine**,** Liver function markers**,** Kidney function markers, toxicity

Introduction

Nanotechnology has provided research-level breakthrough in various industrial applications. Among those it has attained remarkable levels with in medicine are bio-diagnostics, drug delivery and cancer therapy (Ferrari, 2005; Rosi and Mirkin, 2005; Gunasekera *et al.,* 2009). These breakthroughs were from the use of nanomaterials such as nanoparticles. Nanoparticles are microscopic particles with at least one dimension on the nanometer scale (1-100 nm) (Nagarajan and Hatton, 2008). Nanoparticle research is currently an area of intense scientific research, which is due to a wide variety of promising applications in biomedical, optical, and electronic fields (Nagarajan and Hatton, 2008). Examples of metal nanoparticles include silver, gold and platinum nanoparticles (Sulaiman *et al*., 2015a, Sulaiman *et al*, 2015b, Adeyemi *et al*., 2016, Adeyemi and Sulaiman, 2015).

Silver nanoparticles as an arch product from the field of nanotechnology, has gained interest because of its distinctive properties, such as good

conductivity, chemical stability, catalytic, antibacterial activity, antifungal, anti-viral and anti-inflammatory activities (Mukherjee *et al*., 2001; Sondi and Branka, 2004; Chen and Schluesener, 2008, Sulaiman *et al*., 2015a, Sulaiman *et al*, 2015b, Adeyemi *et al*., 2016, Adeyemi and Sulaiman, 2015). Silver-based medical products, ranging from topical ointments and bandages for wound healing to coated stents, have been proven to be effective in retarding and preventing bacterial infections (Chen, 2007). Recent researches carried out by Sulaiman *et al*., 2015a, Sulaiman *et al*, 2015b, Adeyemi *et al*., 2016, Adeyemi and Sulaiman, 2015 on various nanoparticles has tried to address the initial lack of adequate information regarding the toxicity of these nanoparticles. Hence, this study is carried out to further evaluate the effect of silver nanoparticles on more biochemical parameters in the serum and some selected tissues in albino Wistar rats.

Materials and Methods

Silver Nanoparticles and Colchicine

The Silver nanoparticles (AgNPs) used for these experiment was obtained from Sigma Aldrich, Germany. It is a colourless and odourless compound with 20 nm/ml concentration in aqueous buffer and it was delivered in a golden brown bottle. The preparation procedures and characterization have been previously reported (Sulaiman *et al*., 2015a, Sulaiman *et al*, 2015b, Adeyemi *et al*., 2016, Adeyemi and Sulaiman, 2015, Adeyemi and Whiteley, 2013, 2014). The Colchicine used for negative control in this experiment was obtained from Zoology Department, University of Ilorin, Ilorin Nigeria. It's a white capsule-shaped tablet that is soluble in water.

Chemicals and Reagents

The assay kits for Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), urea, albumin (ALB), creatinine (CREA) were products of Randox Laboratories Limited, Antrim, United Kingdom. All other reagents and chemicals used were of analytical grade and supplied by Sigma Aldrich Inc., St. Louis, USA.

Experimental Animals

Eighteen (18) healthy adult male albino rats weighing approximately 138.5 ± 11.5g were obtained from the Animal House of Biochemistry Department of University of Ilorin, Ilorin Nigeria. The animals were housed in well ventilated plastic cages with saw dust as beddings and fed on standard rat feed and allowed access to clean water. The animals were acclimatized for 2 weeks, they were maintain under standard conditions of 12 hours light and dark cycle, handling of animals was humane and consistent with relevant guideline as approved by the institutional ethics committee on scientific study.

Animal Grouping

The albino rats (Rattus *norvergicus*) used for the study were put into six groups each with three rats as shown below:

Group A served as positive control and was administered with 0.5 ml distilled water.

Group B was administered with 0.5 mL of 1.11 mg/kg body weight of Ag nanoparticles dissolved in distilled water

Group C was administered with 0.5 mL of 1.48 mg/kg body weight of Ag nanoparticles dissolved in distilled water

Group D was administered with 0.5 mL of 1.85 mg/kg body weight of Ag nanoparticles dissolved in distilled water

Group E was administered with 0.5 mL of 2.22 mg/kg body weight of Ag nanoparticles dissolved in distilled water

Group F was administered with 0.5 ml of Colchicine (Negative Control) dissolved in distilled water

Blood Collection and Isolation of Organs of Interest

The rats in groups A-E were sacrificed on the day of their last exposure while group F was sacrificed 6 hours after administration. They were weighed and sacrificed by anaesthetizing in a jar containing cotton wool soaked with diethyl ether. In an unconscious state, each rats jugular veins was punctured and blood sample was collected in an EDTA-coated sample bottles after which organs (kidneys, heart and liver) of interest were collected via dissection, weighed and preserved each in 5 mls of 0.25M sucrose solution in preparation for homogenization and centrifugation.

Biochemical Parameters

The activities of Alanine aminotransaminase (ALT) (E.C. 2.6.1.2), Aspartate aminotransaminase (AST) (E.C. 2.6.1.1), Alkaline Phosphatase (ALP) (E.C.3.1.3.1), Albumin, (ALB) CREA Creatinine and Urea (UREA) were assayed using the Randox assay kits (Randox Laboratory Limited) as previously described by Sulaiman *et al*., 2015a, Sulaiman *et al*, 2015b, Adeyemi *et al*., 2016, Adeyemi and Sulaiman, 2015. The protein contents of the serum and homogenates were determined using the Biuret method as previously described by Sulaiman and Adeyemi (2010). All measurements were done using a Spectronic 21 spectrophotometer (Bausch and Lomb, Rochester, NY, USA).

Statistical Analysis

All numerical data were subjected to statistical analysis. The group mean ± S.E.M were calculated for each data and significant differences between were evaluated using one way analysis of variance (ANOVA). Post-test analysis were done using the Duncan Multiple Range at 99.5% significance level (α=0.05).

Results

Average Body Weight

Table 1 shows the effects of silver nanoparticles on weight (g) of wistar rats. From the table, there were no significant differences (P>0.05) in the

weights of the rats of each group over the weeks when compared with the control group.

Weight of Organs

Table 2 shows the effects of silver nanoparticles and negative control (colchicine) on weight of organs. There were no significant differences ($P>0.05$) in the liver and kidney of the positive control and other groups.

For the heart weight, there was no significant difference ($P>0.05$) between the positive control group administered with various concentrations of silver nanoparticles. However, there was significant increment ($P<0.05$) in the group administered colchicine compared with the positive control.

Organ-Body Weight Ratio

Table 3 shows the effects of silver nanoparticles and negative control (colchicine) on Organ Body-Weight ratio. There were no significant differences ($P>0.05$) in liver, kidney and heart of all the groups compared with the positive control group.

Alanine Transaminase (ALT)

Table 4 shows the ALT Activity (U/I) in the serum and selected tissues of rats administered with silver nanoparticles and colchicine (reference drug). The ALT activities were significantly higher ($p<0.05$) in the serum of rats administered with reference drug (20.18) and silver nanoparticles (7.56, 9.52, 10.95 and 14.04) when compared with the control (4.29). However, there was a significant reduction ($p<0.05$) in the ALT activities of the serum of rats treated with silver nanoparticles (7.56, 9.52, 10.95 and 14.04), compared with reference drug (20.18).

The ALT activities were significantly lower ($p<0.05$) in the liver of rats exposed to silver nanoparticles (41.85, 37.98, 35.83 and 34.64) and reference drug (33.39) when compared with the control (50.3). Also, there were significant reduction ($p<0.05$) in the ALT activities of the liver of the rats treated with reference drug (33.39) compared with silver nanoparticles (41.85, 37.98, 35.83 and 34.64).

The ALT activities were significantly lower ($p<0.05$) in the heart of rats administered with silver nanoparticles (26.54, 26.72, 29.11 and 29.52) and reference drug (35.77) when compared with the control (42.14). Also, there were significant reductions ($p<0.05$) in the ALT activities of the heart of the rats administered with silver nanoparticles (26.54, 26.72, 29.11 and 29.52), compared with reference drug (35.77).

Aspartate Transaminase (AST)

Table 5 shows the AST Activity (U/I) in the serum and selected tissues of rats administered silver nanoparticles and colchicine (reference drug). The AST activities were significantly higher ($p<0.05$) in the serum of rats administered with reference drug (244.10) and silver nanoparticles (215.90, 222.30, 242.00 and 241.30) when compared with the positive control (20.14). However, there was a significant reduction ($p<0.05$) in the AST activities of the serum of rats treated with silver nanoparticles (215.90, 222.30, 242.00 and 241.30) to reference drug (244.10)

The AST activities were significantly lower ($p<0.05$) in the liver of rats exposed to silver nanoparticles (151.90, 151.30, 151.50, 153.00) and reference drug (145.70) when compared with the positive control (204.60). Also, there were significant reduction ($p<0.05$) in the ALT activities of the liver of the rats treated with reference drug (145.70) compared with silver nanoparticles (151.90, 151.30, 151.50, 153.00)

The AST activities were significantly lower ($p<0.05$) in the heart of rats exposed to silver nanoparticles (114.20, 98.27, 94.91 and 81.88) and reference drug (67.10) when compared with the positive control (119.60). Also, there were significant reductions ($p<0.05$) in the AST activities of the heart of the rats administered with reference drug (67.10) compared with silver nanoparticles (114.20, 98.27, 94.91 and 81.88)

The AST activities were significantly lower ($p<0.05$) in the kidney of rats exposed to silver nanoparticles (25.37, 22.61, 20.87 and 18.40) and reference drug (13.18) when compared with the positive control (33.33). Also, there were significant reductions ($p<0.05$) in the AST activities of the heart of the rats administered with reference drug (13.18) compared with silver nanoparticles (25.37, 22.61, 20.87 and 18.40).

Alkaline Phosphatase (ALP)

Table 6 shows the ALP Activity (U/I) in the serum and selected tissues of rats administered silver nanoparticles and colchicine (reference drug). The ALP activities was significantly higher ($p<0.05$) in the serum of rats administered with reference drug (259.06) and silver nanoparticles (148.74, 247.47, 253.28 and 249.50) when compared with the positive control (37.12). However, there were no significant differences ($p<0.05$) in the ALP activities of the serum of rats treated with silver nanoparticles group C-E (247.47, 253.28 and 249.50) and reference drug (259.06).

The ALT activity was significantly lower ($p<0.05$) in the liver of rats exposed to silver nanoparticles (142.68, 102.53, 70.45 and 56.82) and reference drug (36.11) when compared with the positive control (166.16). Also, there were significant reduction ($p<0.05$) in the ALP activities of the liver of the rats administered with reference drug (36.11) compared with silver nanoparticles (142.68, 102.53, 70.45 and 56.82).

The ALP activity was significantly higher ($p<0.05$) in the liver of rats exposed to silver nanoparticles (49.49, 13.13, 171.46 and 215.15) and reference drug (237.63) when compared with the positive control (227.78). Also, there were significant reductions ($p<0.05$) in the ALT activities of the heart of the rats administered with silver nanoparticles (49.49, 13.13, 171.46 and 215.15) compared with reference drug (237.63).

Total Protein

Table 7 shows the protein concentration in the serum and selected tissues of rats administered silver nanoparticles and colchicine (reference drug). The protein concentration was significantly higher ($p<0.05$) in the serum of rats treated with silver nanoparticles (4.977, 5.530, 6.180 and 6.487) and reference drug (7.567) when compared with the control (1.802). However, there were significant reduction ($p<0.05$) in the protein concentration of the serum of rats treated with silver nanoparticles (4.977, 5.530, 6.180 and 6.487) compared with reference drug (7.567).

The protein concentration was significantly lower ($p<0.05$) in the liver of rats exposed to silver nanoparticles (5.929, 5.699, 6.011 and 6.016) and reference drug (5.960) when compared with the positive control (6.482).

Also, there were no significant differences ($p<0.05$) in the protein concentration of the liver of the rats administered with silver nanoparticles (5.929, 5.699, 6.011 and 6.016) compared with the reference drug (5.960).

The protein concentration was significantly lower ($p<0.05$) in the heart of rats administered with silver nanoparticles (1.126, 0.973, 0.819 and 0.737) and reference drug (0.568) when compared with the control (2.360). Also, there were no significant differences ($p<0.05$) in the protein concentration of the heart of the rats administered with silver nanoparticles (1.126, 0.973, 0.819 and 0.737) and the reference drug (0.568).

The protein concentration was significantly lower ($p<0.05$) in the kidney of rats administered with silver nanoparticles (0.603, 0.604, 0.461 and 0.450) and reference drug (0.271) when compared with the positive control (0.819). Also, there were no significant differences ($p<0.05$) in the protein concentration of the kidney of the rats administered with silver nanoparticles (0.603, 0.604, 0.461 and 0.450) compared with the reference drug (0.271).

Albumin

Table 8 shows the albumin concentration in the serum and selected tissues of rats administered silver nanoparticles and colchicine (reference drug). The albumin concentration was significantly lower ($p<0.05$) in the serum of rats treated with reference drug (2.257) and silver nanoparticles (1.472, 1.575, 1.593 and 1.744) when compared with the positive control (0.808). However, there were significant reduction ($p<0.05$) in the albumin concentration of the serum of rats treated with silver nanoparticles (1.472, 1.575, 1.593 and 1.744) compared with reference drug (2.257).

The albumin concentration was significantly lower ($p<0.05$) in the liver of rats exposed to silver nanoparticles (0.384, 0.377, 0.249 and 0.212) and reference drug (0.092) when compared with the positive control (0.850). Also, there were significant reductions ($p<0.05$) in the protein concentration of the liver of the rats administered with reference drug (0.092) compared with silver nanoparticles (0.384, 0.377, 0.249 and 0.212)

Urea

Table 9 shows the urea concentration in the serum and selected tissues of rats administered with silver nanoparticles and colchicine (reference drug). The urea concentration was significantly higher ($p<0.05$) in the serum and of rats administered with silver nanoparticles (31.32, 40.35, 52.63 and 60.96) and reference drug (61.53) when compared with the control (13.06). However, there were significant reduction ($p<0.05$) in the ALP activities of the serum of rats treated with silver nanoparticles (31.32, 40.35, 52.63 and 60.96) compared with reference drug (61.53).

There was no significant difference ($p<0.05$) in the urea concentration of liver of rat administered with silver nanoparticles (66.03, 66.27, 65.45 and 65.18), reference drug (65.97) and control (64.30). The urea concentration was significantly higher ($p<0.05$) in the kidney of rats administered with silver nanoparticles (59.97, 50.16, 44.16 and 40.87) and reference drug (35.44) when compared with the control (77.42). Also, there were significant reductions ($p<0.05$) in the urea concentration of the kidney of the rats administered with reference drug (35.44) compared with the silver nanoparticles (59.97, 50.16, 44.16 and 40.87).

Creatinine

Table 10 shows the creatine concentration in the serum and selected tissues of rats administered silver nanoparticles and colchicine (reference drug). The creatinine concentration was significantly higher ($p<0.05$) in the serum of rats treated with reference drug (0.815) and silver nanoparticles (0.439, 0.501, 0.690 and 0.753) when compared with the control (0.251). However, there were significant reduction ($p<0.05$) in the creatinine concentration of the serum of rats treated with silver nanoparticles (0.439, 0.501, 0.690 and 0.753) compared with reference drug (0.815)

The creatinine concentration was significantly lower ($p<0.05$) in the kidney of rats exposed to silver nanoparticles (6.670, 4.930, 3.680, 2.990) and reference drug (1.610) when compared with the positive control (8.050). Also, there were significant reductions ($p<0.05$) in the creatinine concentration in the kidney of the rats administered with reference drug

(1.610) compared with rats treated with silver nanoparticles (6.670, 4.830, 3.680 and 2.990).

Table 1: Average Weight of Wister Rats following oral administration of silver nanoparticles over a period of 5 weeks

	Average weight (g)				
Group	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**
Positive control	189.00±6.51[a]	190.67±8.09[a]	183.67±9.24[a]	167.67±4.98[a]	169.00±1.53[a]
Ag 1.11 mg/kg	79.00±6.56[a]	189.67±7.36[a]	185.33±5.24[a]	170.00±4.58[a]	170.00±6.11[a]
Ag 1.48 mg/kg	172.33±1.86[a]	186.33±2.03[a]	202.00±2.89[a]	189.00±11.59[a]	164.67±31.01[a]
Ag 1.85 mg/kg	167.33±11.22[a]	192.00±10.12[a]	210.00±15.31[a]	176.00±20.61[a]	197.33±18.10[a]
Ag 2.22 mg/kg	178.67±8.35[a]	177.67±8.35[a]	174.67±10.35[a]	188.00±9.82[a]	199.33±10.68[a]

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 2: Rat organ weights following oral administration of silver nanoparticles

	Rat organ weights (g)		
Group	**Liver**	**Heart**	**Kidney**
Positive control	6.52±0.31[a]	0.77±0.07[a]	0.64±0.01[a]
Ag 1.11 mg/kg	6.85±0.34[a]	0.73±0.01[ab]	0.67±0.05[a]
Ag 1.48 mg/kg	8.24±0.25[a]	0.76±0.02[a]	0.68±0.01[a]
Ag 1.85 mg/kg	7.36±1.10[a]	0.67±0.03[ab]	0.59±0.10[a]
Ag 2.22 mg/kg	7.52±0.48[a]	0.73±0.01[ab]	0.68±0.01[a]
Colchicines	6.41±0.57[a]	0.59±0.07[b]	0.62±0.07[a]

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 3: Percentage organ/body weight ratios of Wistar rats orally administered with silver nanoparticles

	Percentage organ/body weight ratios (g)		
Group	**Liver**	**Heart**	**Kidney**
Positive control	3.40±0.19[a]	0.40±0.03[a]	0.33±0.01[a]
Ag 1.11 mg/kg	3.36±0.15[a]	0.35±0.01[a]	0.32±0.02[a]
Ag 1.48 mg/kg	4.04±0.28[a]	0.38±0.01[a]	0.34±0.02[a]
Ag 1.85 mg/kg	3.78±0.36[a]	0.44±0.07[a]	0.32±0.01[a]
Ag 2.22 mg/kg	3.81±0.26[a]	0.37±0.02[a]	0.34±0.02[a]
Colchicines	3.69±0.34[a]	0.34±0.02[a]	0.35±0.03[a]

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 4: Effect of silver nanoparticles on the activity of alanine transaminase (ALT) in rat serum and tissues

	ALT (U/L)		
Group	**Serum**	**Liver**	**Heart**
Positive control	4.285± 0.372[a]	50.3±1.613[a]	42.14±2.331[a]
Ag 1.11 mg/kg	7.559±0.315[b]	41.85±4.813[b]	26.54±5.081[b]
Ag 1.48 mg/kg	9.522±2.177[bc]	37.98±3.067[b]	26.72±0.670[b]
Ag 1.85 mg/kg	10.95±0.990[cd]	35.83±1.994[b]	29.11±0.882[b]
Ag 2.22 mg/kg	14.05±0.362[de]	34.64±1.347[b]	29.52±0.834[b]
Colchicines	20.18±4.747[e]	33.39±1.927[b]	35.77±1.328[c]

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver.

Table 5: Effect of silver nanoparticles on the activity of aspartate transaminase (AST) in rat serum and tissues

	AST (U/L)			
Group	Serum	Liver	Heart	Kidney
Positive control	20.14± 1.633[a]	204.6±1.535[a]	119.6±2.231[a]	33.33±1.671[a]
Ag 1.11 mg/kg	215.9±14.71[b]	151.9±9.876[b]	114.2±5.782[a]	25.37±0.951[b]
Ag 1.48 mg/kg	223.0±6.490[b]	151.3±9.288[b]	98.27±1.579[b]	22.61±0.907[bc]
Ag 1.85 mg/kg	242.0±11.32[b]	151.5±5.889[b]	94.91±2.120[b]	20.87±1.005[cd]
Ag 2.22 mg/kg	241.3±10.73[b]	153.0±8.233[b]	81.88±0.522[c]	18.40±1.131[d]
Colchicines	244.1±3.683[b]	145.7±6.739[b]	67.10±1.517[d]	13.18±1.467[e]

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 6: Effect of silver nanoparticles on the activity of alkaline phosphate (ALP) in rat serum and tissues

	ALP (U/L x10^2)		
Group	Serum	Liver	Kidney
Positive control	37.12± 6.62^a	166.16±2.49^a	227.78±3.22^a
Ag 1.11 mg/kg	148.74±23.78^b	142.68±3.40^b	49.49±13.60^a
Ag 1.48 mg/kg	247.47±2.41^c	102.53±1.77^c	13.13±31.32^b
Ag 1.85 mg/kg	253.28±3.34^c	70.45±4.73^d	171.46±26.07^{bc}
Ag 2.22 mg/kg	249.50±0.91^c	56.82±5.25^e	215.15±24.34^{cd}
Colchicines	259.06±6.85^c	36.11±3.64^f	237.63±7.19^d

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 7: Effect of silver nanoparticle on the level of total protein in rat serum and liver

	Total protein (U/l)			
Group	Serum	Liver	Heart	Kidney
Positive control	1.802 ± 1.633^a	6.482±0.191^a	2.360±0.223^a	0.819±0.075^a
Ag 1.11 mg/kg	4.977±14.71^b	5.929±0.009^b	1.126±0.190^b	0.603±0.018^b
Ag 1.48 mg/kg	5.530±6.490^{bc}	5.699±0.326^b	0.972±0.077^b	0.604±0.031^b
Ag 1.85 mg/kg	6.180±11.32^{bc}	6.011±0.013^{ab}	0.819±0.321^b	0.461±0.056^b
Ag 2.22 mg/kg	6.487±10.73^{bc}	6.016±0.074^{ab}	0.737±0.101^b	0.450±0.060^b
Colchicines	7.567±3.683^c	5.960±0.089^{ab}	0.568±0.178^b	0.271±0.023^b

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 8: Effect of silver nanoparticle on the level of albumin (ALB) in rat serum and liver

	ALB (g/dL)	
Group	**Serum**	**Liver**
Positive control	0.808± 0.074[a]	0.805±0.072[a]
Ag 1.11 mg/kg	0.384±0.068[b]	0.387±0.011[b]
Ag 1.48 mg/kg	0.377±0.021[b]	0.377±0.704[b]
Ag 1.85 mg/kg	0.249±0.084[b]	0.249±0.052[bc]
Ag 2.22 mg/kg	0.212±0.015[b]	0.212±0.021[cd]
Colchicines	0.092±0.017[c]	0.092±0.175[d]

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 9: Effect of silver nanoparticle on the level of urea in rat serum, liver and kidney

	UREA (mmol/L)		
Group	**Serum**	**Liver**	**Kidney**
Positive control	13.06± 0.727[a]	64.30±0.796[a]	77.42±2.886[a]
Ag 1.11 mg/kg	31.32±2.733[b]	66.03±0.785[a]	59.97±1.966[b]
Ag 1.48 mg/kg	40.35±0.210[c]	66.27±0.358[a]	50.16±1.442[bc]
Ag 1.85 mg/kg	52.63±6.122[d]	65.45±0.497[a]	44.16±2.489[cd]
Ag 2.22 mg/kg	60.69±0.134[de]	65.18±0.398[a]	40.87±0.944[cd]
Colchicines	61.53±0.463[e]	65.97±0.477[a]	35.44±6.428[d]

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Table 10: Effect of silver nanoparticle on the level of creatinine (CREA) in rat serum and kidney

	CREA (µmol/L)	
Group	Serum	Kidney
Positive control	0.251 ± 0.063^{a}	0.805 ± 0.609^{a}
Ag 1.11 mg/kg	0.439 ± 0.063^{b}	6.6670 ± 0.230^{b}
Ag 1.48 mg/kg	0.501 ± 0.125^{bc}	4.830 ± 0.398^{c}
Ag 1.85 mg/kg	0.690 ± 0.063^{bc}	3.680 ± 0.460^{cd}
Ag 2.22 mg/kg	0.753 ± 0.109^{bc}	2.990 ± 0.230^{d}
Colchicines	0.815 ± 0.126^{c}	1.610 ± 0.230^{e}

Values are expressed as mean ± SEM (n = 3). Values in each column with different superscripts are significantly different ($p < 0.05$). Ag: silver

Discussion

Effects of Silver Nanoparticles on Average body Weight of Rats over Five Weeks of the Experiment

Throughout the weeks of experiment, there was no significant difference between the positive control group and the test groups. Therefore, silver nanoparticles have no effect on the weight of organs and this is in agreement with Maneewattanapinyo *et al.* (2011

Effects of Silver Nanoparticles on Weight of organs

The constriction in the organ may occur as a result of loss of fluid due to permeability effects whereas inflammation may be a consequence of increase in organ body weight ratio (Moore and Dalley, 1999). The administration of silver nanoparticles at all doses has no effect on the weight of liver, heart and kidney of the test rats compared with the control

rats, suggesting that there was no constriction or inflammation of these organs effected by the nanoparticle.

Effects of Silver Nanoparticles on Organ-Body Weight Ratio

Organ-body weight ratio is a useful marker of cellular swelling, atrophy or hypertrophy (Amresh *et al.*, 2008). Therefore, the absence of an effect on the computed organ-body weight ratios suggests that silver nanoparticles have no effect on the Organ-Body Weight ratio.

Alanine Aminotransferase (ALT) Activity (U/I) in Serum and Selected Tissues of Rats Administered Silver Nanoparticles

The measurement of ALT levels in human serum has proved to be a valuable indicator of liver function in clinical settings (Huang *et al*., 2006). The aminotransferases (ALT and AST) are 'markers' of liver damage and can thus be used to assess liver cytolysis with ALT being a more sensitive biomarker of hepatotoxicity than AST (Pramyothin *et al*., 2006). The reduction in the activity of the ALT of the liver, heart and kidney of rats administered with varying concentrations of silver nanoparticles indicated a possible toxic effect as a result of the case of high concentrations of silver nanoparticles as supported by Chen *et al*. (2007). The alterations to the levels of enzymes may represent adaptive mechanisms by the animals trying to offset stress imposed by exposure to the silver nanoparticles (Yang *et al.*, 2009).

Aspartate Transaminase (AST) Activity (U/I) in the Serum and Selected Tissues of Rats Administered Silver Nanoparticles

The aminotransferases (ALT and AST) are 'markers' of liver damage and can thus be used to assess liver cytolysis (Pramyothin *et al*., 2006). Although AST is commonly included clinically as part of a diagnostic liver function test, AST has a broader clinical utility since it may also be elevated in diseases affecting other organs, such as the heart or muscles in myocardial infarction, also in acute pancreatitis, acute hemolytic anemia, severe burns, acute renal disease, musculoskeletal diseases and trauma (Kim *et al*., 2008). The decreased AST activities in the liver and heart of rats treated with high quantities of silver nanoparticles (1.850 mg and 2.220 mg) depicts that the tissues have been compromised and that AST

might have leaked into the serum. This is in agreement with the work done by Maneewattanapinyo *et al*. (2011).

Alkaline Phosphatase Activities of Selected Tissues of Rats Administered Silver Nanoparticles

In humans, ALP is present in all tissues throughout the body, but is particularly concentrated in liver, bile duct, kidney, bone, intestinal mucosa and the placenta (Thomas *et al.,* 2002). ALP is a 'marker' enzyme for the plasma membrane and endoplasmic reticulum (Wright and Plummer, 1974) and is often used to assess the integrity of the plasma membrane and endoplasmic reticulum (Akanji *et al*., 1993). Administrations of high concentrations of silver nanoparticles indicated significant reduction in the ALP levels of liver and kidney. In agreement, a previous study done by Kim *et al,*. (2009) demonstrated that administration of silver nanoparticles to rats caused significant reductions to the ALP levels of the selected organs studied.

Protein Concentration in the Serum and Liver of Rats Administered Silver Nanoparticles

The concentration of total protein is a useful 'marker' of secretory, synthetic and excretory functioning of the liver (Yakubu and Musa, 2012). The increase in the total protein content in the serum suggests a compromise of the synthetic ability of the liver (Akanji *et al*., 2013). The reduction in the protein concentration in the rats treated with silver nanoparticle indicates hyper proteinemia indicating deamination of protein.

Albumin Concentration (g/dl) in Serum and Liver of Rats Administered Silver Nanoparticles

Albumin is the major plasma protein. Molecular weight is approximately 66.3kDa. It is synthesized exclusively in the liver. A falling concentration in chronic liver disease suggests a clinically significant deterioration in liver function 'decompensation' (ACB, 2012). The concentration of albumin is a useful 'marker' of secretory, synthetic and excretory functioning of the liver and kidney (Yakubu and Musa, 2012). Thus, the decreased albumin concentration in the liver of rats treated with various

concentrations of silver nanoparticles depicts that the liver have been compromised and some of the liver albumin might have leaked into the serum.

Urea Concentrations in the Serum and Kidney of Rats Administered Silver Nanoparticles

The significance of the enzyme urease includes: to serve as virulence factor in human and animal infections of the urinary and gastrointestinal tracts, as well as to play role in recycling of nitrogenous wastes in the rumens of domestic livestock. The kidneys regulate the excretion of urea and reabsorption of electrolytes into the blood. Filtration occurs at the glomeruli while reabsorption takes place in the renal tubules (Mayne, 2005). When there is compromise of normal glomerular function, substances normally cleared by the kidneys such as urea accumulate in the biological fluid. The presence of increased level of serum urea in the rats administered with higher concentrations of silver nanoparticles (1.85mg and 2.22mg) indicated that there has been leakage in the kidney that caused the urea to leak from the kidney to the serum.

Creatinine Concentrations in the Serum and Kidney of Rats Administered Silver Nanoparticles

Creatinine is derived from creatine and creatinine phosphate in muscle tissue and may be defined as nitrogenous waste product. Creatinine is re-utilized but it is excreted from the body in the urine via the kidney. It is produced and excreted at a constant rate which is proportional to the body muscle mass. As a consequence of the way in which creatine is excreted by the kidney function. Creatinine is regarded as the most useful endogenous marker in the diagnosis and treatment of kidney disease (Allen, 2012). An elevated level of creatinine in the serum in rats with high concentrations of silver nanoparticles (1.850mg and 2.220mg) indicated that creatinine in the kidney has leaked to the serum. In accordance to this results, Creasey and Moffat, 1973; Danscher, 1981; Ham and Tange, 1972 revealed that the damage in the kidney may be attributed that the uncleared silver that has been shown to be deposited in the renal glomerular basement membrane.

Conclusion

The results obtained suggested that the effects of silver nanoparticles on hepatocytes at high doses (1.85mg/kg and 2.22mg/kg) led to the disruption and leakage of its enzymes into the blood stream. High concentrations of alkaline phosphatase (ALP), Alanine transaminase (ALT) and Aspartate transaminase (AST) were found the serum of the rats, indicating liver damage. We therefore recommend that the usage of silver nanoparticles as drug carrier should be at low doses to prevent hepatotoxicity and other related health issues.

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