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Toxicological Effects on Silver Nanoparticles as Anticarcinogenic Agent and its Treatment with Curcumin

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Abstract

In this study, the efficacy of silver nanoparticles (AgNPs) for treatment the Ehrlich Ascites Carcinoma cells (EAC) and trials to overcome its side effects by administration of the curcumin were carried out. Hundred and fifty mature male albino mice were divided into fifteen equal groups. Negative control animals were I.P injected with sterile normal saline, Positive control: oral dose curcumin daily an oral dose of (400 mg/Kg BW)**,** suspended in dist. H_2O dosed, in the induced cancer control group: mice were inoculated with EAC through serial I/P of 2.5 x 10^6 EAC tumor cells 0.2 ml at 5-8 days intervals**.** Inject I.P. with different doses of silver nanoparticles**,** 100µ AgNPs+induced tumor, 200 µ of AgNPs + tumor induction, l00 µ AgNPs+ curcumin (400 mg/kg) + tumor induction, 200 µ AgNPs + curcumin (400 mg/kg) + tumor induction, 100 µ AgNPs before tumor induction by 15 days , 200 µ AgNPs buffer tumor induction 15 days then tumor induction EAC, 100 µ AgNPs + curcumin 400 µM/kg b.wt.) before induced tumor 15 days then induced tumor EAC, 200 µ AgNPs + curcumin 400 mg/kg bw.t) before induced tumor then tumor induction EAC, 100 µ AgNPs after tumor cell implantation 8 days later, 200 µ AgNPs after tumor cell implantation 8 days later, 100 µ AgNPs + curcumin 400 mg/kg BW) after tumor induction 8 day and 200 µ AgNPs + curcumin 400 mg/kg bw.t) after 8 days tumor induction. All results and histopathologyfindings validated that the silver nanoparticles are good for treatment of EAC and the curcumin can overcome their side effects.

Keywords: Silver Nanoparticles, EAC Cancer Cells, Curcumin

Introduction

Nanotechnology is emerging as a rapidly growing field with its application in science and technology for the purpose of manufacturing new materials like cosmetics, information and communication technology (ICT), food and feed, environmental health and agricultural productions at the nanoscale level [1]. The term Nanotechnology was coined by Professor Norio Taniguchi in Tokyo Science University in the year 1974 to explain precision manufacturing of materials at the nanometer level. Nanotechnology as a branch of science which is related to nano-materials helps in overcoming the limitations of size and can change the outlook of the world regarding science [2]. By manipulating materials at the atomic level, nanotechnology offers to achieve unique properties for various desired applications. It is noticeable that most of the nature's creations occur at the nanoscale regime too [3]. Because of its widespread application, the commercial nanotechnology industry is predicted to increase significantly [4].

The term "Nano" is a Greek word synonymous to dwarf meaning extremely small [5] which is used to indicate one billionth of a meter or 10^{-9}. One of the most natural questions to ask when starting to deal with nanoparticles is: "why are nanoparticles so interesting"? The answer lies in the nature of and unique properties possessed by nanostructures [6]. Nanoparticles are clusters of atoms in the size range of 1-100 nm[7]. Reducing the particle size of materials is an efficient and reliable tool for increasing their biocompatibility. Furthermore, nano-materials can be changed for more efficient applications in different fields such as bioscience and medicine[2]. Among the commercially available nano-sized materials, silver nanoparticles are by far the most used nano-compounds [8].

Silver was known only as a metal until the recent advent of the nanotechnology era, when it became recognized that silver could be produced at the nano-scale using recent engineering technologies. Silver nanoparticles

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(AgNPs) have emerged as an arch product from the field of nanotechnology. Toxicological information on nanoparticles remains insufficient; thus frameworks for future toxicological assessments on nano-sized materials have been promoted [9].

Recent studies suggest that excessive production of reactive oxygen species (ROS) and oxidative stress could be one of the possible mechanisms of nanoparticle toxicity [4]. AgNPs were reported to act via reactive oxygen species (ROS) production and glutathione depletion in mice liver cells [10]. ROS generation has been shown to play an important role in apoptosis induced by treatment with AgNPs [11]. ROS in general cause DNA damage, including a multitude of oxidized base lesions, a basic site, single and double-strand breaks; all of these can be cytotoxic, genotoxic or mutagenic [12]. There are few conventional drugs that can stimulate liver function and offer hepato-protection or help in the regeneration of hepatic cells [13]. Many plant derived natural products have the potential to be hepatoprotective and therefore can be used to treat acute and chronic liver diseases. The challenge is to identify the most promising compounds and evaluate their protective mechanism [14].

Curcumin is a widely used spice and coloring agent in food. It is extracted from the powdered dry rhizome of turmeric (Curcuma longa L.), a perennial herb widely cultivated in tropical regions of Asia. Curcumin is known to have multiple pharmacological properties such as anti-carcinogenic, anti-inflammatory and antioxidant [15]. However, the preventive potential of curcumin against nanoparticles toxicity has not been explored. This study was designed to investigate AgNPs induced cytotoxicity, oxidative stress and apoptosis in mice and evaluate if silver nanoparticles exhibit toxic effects on the liver following intraperitoneal infection. The preventive potential of curcumin against AgNPs induced toxicity was further examined.

Cancer is the second leading cause of death in developing countries as it presently responsible for about 25% of deaths in developed countries and for 15% of all deaths worldwide. It can therefore be considered as one of the foremost health problems, with about 1.45 million new cancer cases being expected yearly, it may be caused due to incorrect diet, genetic predisposition or environmental factors [16]. Cancer chemotherapy is a very difficult task as the problems of chemotherapy are drug resistance, multidrug resistance [17] and one of its main associated another problems is the nonspecific toxicity of most anticancer drugs due to their bio-distribution throughout the body, which requires the administration of a large total dose to achieve high local concentrations in a tumor [18].

The present study aimed to investigate the *in vivo* hepatotoxic effects of silver nanoparticles in mice. Moreover, aimed to study the potential hepatoprotective role of the silver nanoparticles and dietary antioxidant curcumin. For this, the following parameters were analyzed: Biochemical analysis in liver tissues Include, Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), Glutathione reductase (GR), Reduced glutathione (GSH) and Lipid peroxidation: Malondialdehyde (MDA), DNA fragmentation assay and Histopathological studies: Liver.

Material and Methods

Experimental animals

Hundred and fifty adult male Swiss albino mice weighted 30-40 gm. were obtained from the Laboratory Animal Housing Unit, Animal Health, Research Institute, Dokki, Cairo, Egypt. The animals were clinically healthy, kept under hygienic conditions. Housed in metal cages with hard wood shavings as bedding. They were maintained on balanced ration, water and the food were giving ad-libtum throughout the experimental period. The animals were accommodated to the laboratory conditions for one week before beginning of experiment.

Tumor Cell Line: Ehrlich Ascites Carcinoma cells (EAC):

The parent line of Ehrlich Ascites Carcinoma cells was initially supplied by the National Cancer Institute, Cairo University, Egypt, and maintained in female Swiss albino mice through serial intra-peritoneal inoculation of *[EAC]* $2.5x10^6$ tumor cells/0.2 ml at 5-8 day intervals in the laboratory in an ascites form.

Transplantation of Tumor in mice:

EAC cells were collected from moderately growing 5-8 days old donor. After making appropriate dilution, the viability was checked by the trypan blue exclusion test 0.2ml portions of ascetic fluid containing 2.5 $^{X}10^{6}$ viable cells were intraperitoneally injected in a group of healthy mice for maintenance of the line and for experimental work [19].

Silver nanoparticles

Silver nanoparticles (AgNPs) are colloidal silver nanoparticles yellow / grey / opal colored liquid with particle size (33 nm) total diameter with ware length (400 -410 nm), molar weight (8, 93 E+ 07) and molar concentration (2.32 E-10) were purchased for the International Center of nanotechnology, Sadaat University, El Sadaat City- Monifya Province, Egypt.

Curcumin: was purchased from Sigma Co. Cairo Egypt

Table 1: Experimental design

Control Groups	Treated groups
1- Negative control: I.P injection with normal saline 2- Positive control: oral dose curcumin daily an oral dose (400 mg/Kg B. Wt.) according to [19] suspended in dist. H_2O dosed by [20]. 3- Induced cancer control group: mice were inoculated with EAC (Ehrlich Ascites Carcinoma cells) through serial I/P of 2.5 x 10^6 EAC tumor cells 0.2 ml at 5-8 days intervals in the laboratory in an ascites form According to [21].	Inject I.P. with different doses of silver nanoparticles according to [22]. 4- 100µM AgNPs+ induced tumor 5-200 µM of AgNPs + induced tumor 6-l00 µM AgNPs+ curcumin (400 mg/kg) + induced tumor 7- 200 µM AgNPs + curcumin (400 mg/kg) + induced tumor. 8- 100 µM AgNPs before induced tumor 15 days then induced tumor cell. 9- 200 µM AgNPs buffer induced tumor 15 days then induced tumor EAC. 10- 100 µM AgNPs + curcumin 400 µM/kg b.wt.) before induced tumor 15 days then induced tumor EAC. 11- 200 µM AgNPs + curcumin 400 mg/kg bw.t) before induced tumor then induced tumor EAC 12- 100 µM AgNPs after tumor cell implantation 8 days latter. 13-200 µM AgNPs after tumor cell implantation 8 days latter. 14- 100 µM AgNPs + curcumin 400 mg/kg bw.t) after induced tumor 8 day. 15-200 µM AgNPs + curcumin 400 mg/kg bw.t) after induced tumor 8 day.

Preparation of Liver Homogenate

One gram of the liver tissue washed in distilled water then put in homogenized buffer and homogenized separately using a Dounce homogenizer at 4°C. The crude tissue homogenate then centrifuged at 3000 xg for 15 min at 4°C and the supernatant was separated and kept at -20°C till estimation of malondialdehyde (MDA), reduced glutathione (GSH), glutalhione pcroxidase (GPx), glutathione reductase (OR), and catalase (CAT).

Biochemical analysis

The optical densities of the given parameters were measured by Shimudzu type spectrophotometer (UV 120-02) manufactured by Incorporation Kyoto, Japan. Include, Catalase (CAT), Glutathione peroxidase (GPx), Glutathione reductase (GR), Reduced glutathione (GSH), Lipid peroxidation and Malondialdehyde (MDA).

Histopathological studies

Liver samples from all mice were fixed in 10% neutral buffered formalin. Then specimens were prepared for paraffin sections and stained with H&E for histopathological examination under light microscope [23].

Statistical analysis

The results were expressed as means ± S.E.M. All data were done with the Statistical Package for Social Sciences (SPSS 17.0 for windows) [24]. The results were analyzed using one way analysis of variance (ANOVA) followed by Duncan's test for comparison between different treatment groups. Statistical significance was set at $p < 0.05$.

Results and Discussion

Micronucleus test (MN)

There was a significant increase ($P \leq 0.05$) MN frequencies in erythrocyte of silver nanoparticles (AgNPS) treated EAC mice compared with positive infected group. While combined treatment of curcumin and AgNPS significant decrease which non-significant in curcumin group. MDA is the end product of lipid peroxidation and has been used widely as a marker of free radical damage in lipid molecules. Peroxidation of the fatty acids results in MDA production [25]. MDA cause the crosslinking of membrane component by affecting the ion exchange through the cell membrane and change ion permeability of membrane and enzyme activities.

Table 2: Efficacy of silver Nano particles and curcumin induced micronucleus frequency in the erythrocytes blood smear of treated EAC bearing male mice.

	Groups / MN	MN/1000 erythrocytes
1	Infected control	6.48±1.25 [a]
2	Curcumine control	0.75±0.06 [c]
3	AgNPS 100 µM	0.97±0.18 [b]
4	AgNPS 200 µM	1.16±0.22 [b]
5	EgNPS 100+EAC infected	1.36±0.36 [c]
6	AgNPs 200+EAC infected	0.85±0.33 [c]
7	AgNPs+EAC infected +curcumin	0.76±0.15 [c]
8	AgNPS 200 µM+curcumin+infected EAC	0.56±0.11 [b]
9	AgNPS 200 µM AgNPs+ before induced tumes	0.38+0.15 [b]
10	100 µM AgNPs + curcumin 400 µM/kg b.wt.) before induced tumor 15 days then induced tumor EAC.	0.29+0.10 [b]
11	200 µM AgNPs + curcumin 400 mg/kg bw.t) before induced tumor then induced tumor EAC	0.22+0.15 [c]
12	100 µM AgNPs after tumor cell implantation 8 days latter.	0.19+0.05 [c]
13	200 µM AgNPs after tumor cell implantation 8 days latter.	4.25+0.45 [b]
14	100 µM AgNPs + curcumin 400 mg/kg bw.t) after induced tumor 8 day.	3.10+0.20 [b]
15	200 µM AgNPs + curcumin 400 mg/kg bw.t) after induced tumor 8 day.	0.9+0.10 [c]

Mean within the same column carrying different superscripts are significant ($P \leq 0.01$).

GSH, is formed by glutamyl cysteinyl ligas (γ-GCL) and glutathione synthetase (GSS), γ-GCL catalyses the first and the rate –limiting step in the process that yields glutamyl cysteine in cellular GSH biosynthesis. The final final step is catalyzed by GSS and adds a glycine residue to form glutamyl cysteine or glutathione [26].

Silver nanoparticles cause histopathological change in the liver, which indicated the tendency of silver ions to bind the thiol groups in livers causing reduction reactions, transferring of glutathione to bile bladder and reducing the concentration of glutathione available for biochemical reductions. it should be mentioned that reduced glutathione is necessary to remove peroxides [27].

Table 3: The activity of reduced glutathione (GSH) concentration (nmol/mg protein), glutathione reductase (GR) (mmol/gm hepatic tissues) and glutathione peroxidase (GPX) concentration (u/mg protein) in hepatic homogenate of mice in all groups administered silver Nanoparticles (100 or µM) and curcumin against carcinogenicity of EAC cells.

Groups \ Antioxidant enzymes	Reduced glutathione (GSH)	Glutathione reeducates (GR)	Glutathione peroxidase (GPx)
1	42.75±0.44 [c]	18.35±0.39 [d]	70.25±0.70 [c]
2	70.10±1.25 [a]	16.80±0.42 [d]	15.15±0.95 [c]
3	98.75±5.60 [a]	59.10±3.40 [a]	122.25±5.30 [a]
4	45.45±1.30 [c]	29.25±0.40 [c]	92.30±3.65 [b]
5	48.70±1.70 [c]	33.60±0.60 [c]	95.60±3.75 [b]
6	53.90±0.35 [b]	24.30±0.30 [d]	61.30±2.15 [b]
7	55.40±0.60 [b]	27.50±0.52 [d]	64.25±2.35 [b]
8	40.52±0.45 [c]	23.90±0.25 [d]	60.60±1.75 [c]
9	43.30±0.40 [c]	26.60±0.45 [d]	63.40±1.80 [c]
10	37.45±0.35 [c]	20.80±0.30 [d]	58.50±1.50 [c]
11	41.60±0.65 [b]	22.10±0.20 [d]	61.30±1.35 [c]
12	50.40±2.60 [a]	42.70±1.80 [b]	85.60±3.15 [b]
13	56.75±2.85 [a]	46.30±2.20 [b]	88.45±3.45 [b]
14	48.00±0.70 [b]	35.70±1.60 [c]	81.20±3.00 [b]
15	51.50±1.40 [b]	38.30±1.75 [c]	83.55±3.25 [b]

Mean within the same column carrying different superscripts are significant ($P<0.01$).

Reduced glutathione which works as a direct free –radical scavenger, but functions as a substrate for GPX and GST. The decrease in GSH levels might have resulted from the increased utilization by the antioxidant mechanisms. Increased activity of GSHPX and reaction catalyzed by glutathione S-transferase may have a role in the reduction in GSH levels in the treated cells [28].

Oxygen free radical (OFRs) scavenging enzymes respond to conditions of oxidative stress by increasing the anti-oxydative enzyme SODS, GSH-Px and catalase activities that scavenge unwanted O_2, H_2O_2 and –ROOH [29]. Hepatic carcinoma, EAC implanted mices and trials by I/P injection of AgNPS in mice, has possible caused severe irritation of oxidant system in these cells [30]. The live tissue damage in high dosage of Nano-silver particles is probably caused by stimulation of the antioxidant system in these cells by Nano silver injection. Free radicals induced from Nano silver particles attack hepatocyte and cause the release of stored liver enzymes in them and enter the blood serum. Therefore, pathological changes in liver tissue might be due to the accumulation and residue of these Nanoparticles in the tissue [31].

Table 4: Catalase activity (U/mg Protein) and Malondialidhyde (nmol/mg protein) in mice hepatic tissues in all groups administered silver Nanoparticles (100 or 200 mg) and/ curcumin (400 mg/kg b.wt.) agenicity of EAC cells.

Groups \ Antioxidant enzymes	Catalase activity (U/mg protein)	Malondialialdhyde (nmol/mg protein)
1	56.00±0.40 [d]	20.50±0.25 [d]
2	40.45±0.80 [c]	17.80±0.60 [c]
3	81.20±1.85 [b]	42.30±1.50 [b]
4	71.35±0.90 [b]	28.75±0.65 [a]
5	73.50±1.10 [b]	30.60±0.45 [a]
6	60.15±1.40 [b]	32.40±0.55 [a]
7	63.80±0.55 [b]	35.10±0.60 [a]
8	59.45±0.60 [d]	24.65±0.50 [d]
9	61.90±0.75 [d]	26.70±0.65 [d]
10	54.90±0.70 [d]	18.50±0.25 [d]
11	56.15±0.45 [d]	20.35±0.30 [d]
12	69.30±0.75 [c]	35.60±0.80 [c]
13	71.90±1.30 [c]	38.40±1.10 [c]
14	66.30±0.80 [d]	33.60±0.40 [d]
15	68.50±1.20 [d]	36.30±0.45 [d]

Mean within the same column carrying different superscripts are significant ($P \leq 0.01$).

In mice, supplementation with curcumin provided significant antioxidant effects. Curcumin may decrease the production of free radicals which could lead to decreasing hepatic antioxidant enzyme activities catalase, glutathione peroxidase and glutathione reductase in all groups treated with AgNPS (3–15) that resulted in a significant reduction in lipid peroxidation.

Regarding to the histopathological changes there were several in the mice liver revealed that the inflammatory phase begun within 5 – 8 days after EAC cells implantation while the proliferative phase showed fibroblast proliferation and granulation tissue (Fibrovascular) formation at the 8^{th} day and the remodulation phase revealed scar formation with rearrangement of regenerated hepatocyte at the sometime and pre-implantation of AgNPS 15 days and enhances of repithelization. The positive control mice liver were implanted with EAC cells revealed that focal coagulative necrosis of the hepatic parenchyma with various degenerative changes varied from cloudy swelling to hydropic degeneration. This hepatic capsule (protenitis) could be seen with numerous newly formed bile ductules in portal area (Fig. 1-4) in agreement with [32]. The liver of mice implanted with EAC cells and treated with 100 µM AgNPS at the same time revealed hepatic cells suffered from reversible hydropic degeneration with interstitial mononuclear cells infiltration and kuffer's cells usually appear hyperplasia.

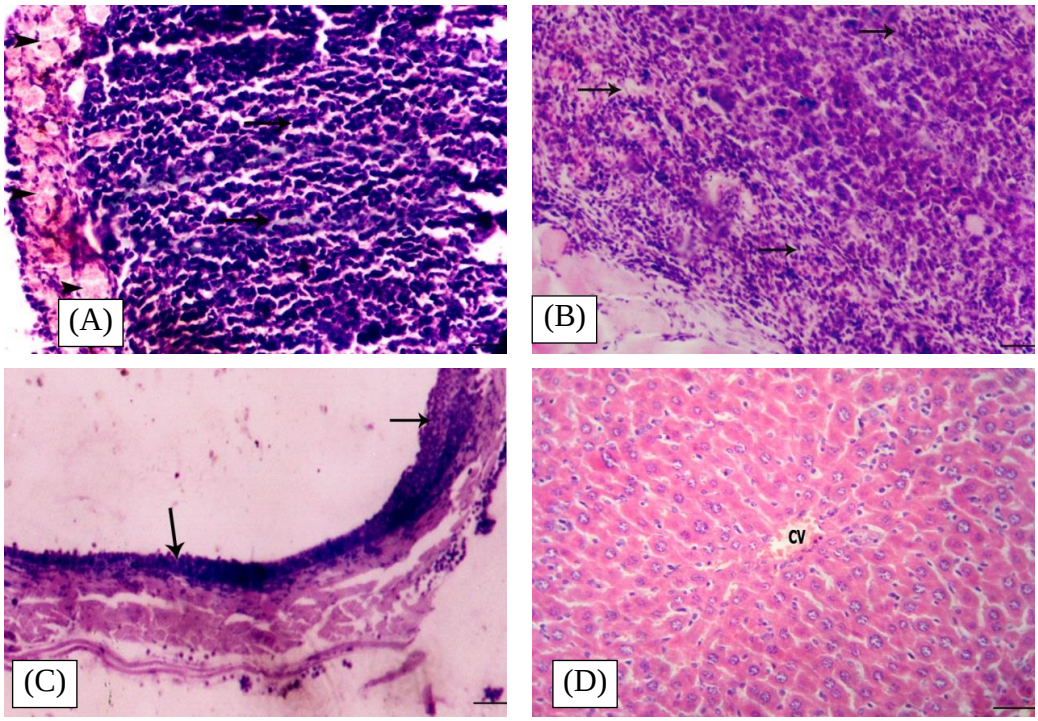

Figure 1 A. Liver of mice implanted with EAC cell and treated with 100 µM AgNPs at the same time revealed hepatic cells suffered from reversible hydropic degeneration with interstitial mononuclear cell infiltration. Kupffer's cells usually appear hyperplasia. (Negative control, bar =100 µM) (H & E). B. Liver of mice implanted with EAC cell and treated 100 µM AgNPs at the same time and curcumin (400 mg/kg), the hepatic blood vessels and sinusoids showed slight congestion, cloudy swelling and hydropic degeneration were common. C. Liver of mice implanted with EAC cells and treated 100 µM AgNPs before implantation and curcumin 15 days before appeared interstitial and portal leucocytic aggregation mainly lymphocyte with normal hepatic cells. Hyperplastic kupffer's cells and mild congestion of the blood (Bar=100 µM) (H & E).
D. Liver of mice implanted with EAC cells and treated with 100 µM AgNPs after implantation 8 days revealed lymphocyte with karyo and cytomeggally besides extramedullary hematopoiesis. (Bar =100 µM) (H & E).

Conflict of interest

The authors declare that they have no conflict of interest

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الملخص العربى

دراسة التأثيرات النانونية لسمية جزيئات الفضة النانوية كمضاد للسرطان وعلاجها بالكركم

مجدى فكرى ابو الفتوح ، على حيدر ابو حديد و اسراء غريب قطب

قسم الطب الشرعى والسموم - كلية الطب البيطري - جامعة الزقازيق

تم استخدام جزيئات الفضة النانونية المتناهية الصغر (١-١٠ نانو متري) بجرعات (١٠٠ – ٢٠٠ نانو مل) فى مائة وخمسون فأراً أبيض ذكر بالغ. تم تقسيمها الى خمسة عشر مجموعة وتم حقن الأنسجة السرطانية فى مجموعات حتى يتسنى لنا محاولة استخدام الفضة النانوية للعلاج وتم استخدام الكركم (٤٠٠ ملجرام/كجم) لمحاولة التغلب على الأثار الجانبية للفضة النانونية على الكبد للحيوانات التى تم علاجها. وتم قياس انزيمات الأكسدة فى الخلايا الكبدية وجد أن جميع النتائج تؤكد أن الفضة النانونية لها تأثير كبير فى علاج الخلايا السرطانية بالإضافة أن الكركم قلل من الأثار الجانبية لتأثير الفضة النانونية وتم تأكيده عن طريق تحليل الإنزيمات الكبدية (MDA, CAT, GSH, GR, GPx)