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RESEARCH ARTICLE

Preparation of Fe_3O_4-Au @ Fe_3O_4-Ag Composite Nanoparticles and Cytotoxicity Study of kidney parameters in mice

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ABSTRACT

Magnetic Fe_3O_4 nanoparticles covered with gold and silver particles were prepared by hydrothermal method, and for the successful coating of gold and silver particles on Fe_3O_4 surface, the nanoparticles showed good dispersion and solubility in the physiological phase. Characterization was carried out on the nanoparticles that were obtained using X-ray diffraction, transmission electron microscopy, and vibration sample magnetometry (VSM). (Fe_3O_4-Au @ Fe_3O_4-Ag) nanoparticles are between 8 and 22 nm and 4 to 16 nm in size, respectively, exhibiting supermagnetism and highly saturated magnetization at room temperature. Also, available data on in vivo toxicity are limited. The advantage of the current study is to evaluate the toxicity of (Fe_3O_4-Au @ Fe_3O_4-Ag) nanoparticles by morphological and functional criteria. The biochemical parameters of the organism were also evaluated using an animal model. MNPs were injected intraperitoneally for (7, 14, 21 and 28) days. In addition, histological examination was studied in kidney samples. Our results also show that there are no significant changes in biochemical parameters. Where the tissue was kept without any change during the entire period when monitoring. As well as no significant body weight occurred during the testing period and after MNPs particle injection.

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INTRODUCTION

Nanoparticles have many physical, chemical and biological properties, are specific in shape and size, and have a high surface-to-volume ratio. These particles are also very suitable for use in various biological and medical fields, as well as in contrast media for drug delivery[1], damaged tissue repair, cellular therapies[2], immunoassays[3], hyperthermia[4], and magnetic resonance imaging [5] as well. Nanoparticles are composed of elements that have magnetic properties such as nickel, iron and cobalt, all of which show magnetic properties as they are called (magnetic nanoparticles)[6]. There have been developments and work on new processes as the fields of tumor hyperthermia and further studies because the novel is nanomaterials, biomedicine and applications. More than a rework of the design of nanoparticles and nanocomposites for use in hyperthermia. In the development of the use of nanoparticle compounds, such as super-magnetic core-shell particles, There is also a great interest in gravity because it combines the advantages in heterogeneous materials[7], as well as silver (Ag) and gold (Au) particles were used to encapsulate iron nanoparticles. There is also excellent near infrared (NIR) radiation, as well as light sensitivity and strong absorption capacity in the silver and gold layer (Fe_3O_4 –Au@ Fe_3O_4–Ag) that makes it useful in heat treatment used in medical applications [8,9]. There are also many recent studies working on encapsulation of iron nanoparticles using gold and silver particles, as well as biocompatibility in a biomedical application to the body of an organism that is a guarantee in clinical

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uses safe in this type of heterogeneous materials is still limited [10,14]. Where essential criteria in their clinical applications are safety and very good biocompatibility, which are distinct and important properties in the manufacture of nanomedicine. Also, the authors have now done recent research on Fe_3O_4 and Fe_2O_3 magnetic nanoparticles by using them as a pathological heat therapy in a cell line as an animal model in kidney and liver cancer through magnetic fluid hyperthermia (MFH)[15,16], as well as no histotoxicity in tissues or organs treated by nanoparticles. In this study of a crystalline crust for high current and monodispersion, The Fe_3O_4–Au@Fe_3O_4–Ag multifunctional has a magnetic compound and is synthesized by nanoparticles and is used by high temperature in magnetic field. liquid in addition to a semi-inductive high temperature. The production and formation of a basic structure in the shell takes place in two sequential steps, the core (Fe_3O_4) is coated using the coating of gold and silver particles[17,18]. Where well-engineered composite magnetic nanoparticles (Fe_3O_4–Au@ Fe_3O_4–Ag) tend to be collected in tumors because of their unbound nature in malignant blood vessels, and they are injected into a tumor affected organ and have a very high thermal effect in response and less impact under an alternating magnetic field (AMF) and are exposed to laser rays (NIR) and it is possible to have an effect that can be directed by heating on any tumor without damage to healthy tissues[19,20]. It is also possible to note the peacefulness of the complex group (MNPs) and they are biocompatible. As a result, all biocompatibility and toxicity (*in vivo* and *in vitro*) need to be evaluated by (Fe_3O_4 –Au@ Fe_3O_4–Ag), which is a potential for application in high temperature research. Thus, hemolysis, cytotoxicity assay, and micronucleus assay, as well as severe toxicity present in mice were detected to evaluate biocompatibility of magnetic nanoparticles in self-assembling compounds (Fe_3O_4–Au@ Fe_3O_4–Ag) and be in this research[21].

EXPERIMENTAL

Chemicals and materials

Sodium borohydride ($NaBH_4$), Silver nitrate($AgNo_3$), ethanolamine, ethylene glycol, ferric chloride hexahydrate (FeCl3•6H2O), and anhydrous sodium acetate (NaOAc) are the components of this compound (ETA), Sodium borohydride ($NaBH_4$), Silver nitrate($AgNo_3$), Sodium Citrate($Na_3C_6H_5O_7$), ($HAucl_4$), Beijing Chemicals was the vendor for the purchase of both ethanol and and (Beijing, China). All of the chemical agents are of an analytical grade and are utilized directly without undergoing any additional purification..

Synthesis of bare Fe_3O_4 MNPs

We prepared the bare Fe_3O_4 MNPs in a hydrothermal method. In order to create the orange-colored stable solution, first approximately 1.5 grams of FeCl3 • 6H2O were dissolved in 40 milliliters of equal parts solvent (20 milliliters each) of EG and ETA. In addition, we formed a homogeneous solution by continuously magnetically mixing 4.0 grams of NaOAc into the orange-colored solution while it was being stirred, and then we transferred the solution to an autoclave made of Teflon-lined stainless steel (100 ml) and closed for heating at 200 ° C. Upon completion of the 10-hour heating, we cooled the autoclave to naturally ambient temperature. We then washed magnetic nanoparticles with ethanol and deionized water (DW) respectively, and then dried them at 60°C overnight.

Synthesis of core- shell Fe_3O_4-Au MNPs .

In order to prepare Fe_3O_4-Au, we suspended iron oxide nanoparticles in $HAuCl_4$ solution, by continuous stirring. We prepared)100ml(from sodium citrate (2.29 g/ml) and heat at (90°C). Hence, we add (40mg) of Fe_3O_4 NPs directly to solution. about (5ml) of $HAuCI_4$ solution (0.01 mol/L) was also add and heat for (15) minutes before the cooling at room temperatures with vigorous stirring from (15 to 20) minutes. We isolated the obtained colloidal solution by means of a magnetic field. We also washed the Fe_30_4-Au NPs, magnetically separated them and suspended them in)20ml(doubly deionized water.

Synthesis of core- shell Fe_3O_4-Ag MNPs .

The Fe_3O_4-Ag nanoparticles were produced by reducing Ag ions in the presence of Fe_3O_4 nanoparticles during the synthesis process. We began by incorporating 20 milliliters of 0.064 millimolar $AgNO_3$ into a 70 milliliter suspension that already contained 1 gram of Fe304 nanoparticles. After illuminating 5 minutes of mixing, we incorporated 50 milliliters of 0.32 millimolar $NaBH_4$ into the mixture in a drop-by-drop manner. with a lack of clarity. After adding the NaBH4 while the mixture was at room temperature,

we mixed it for a further ten minutes. This will result in the formation of Fe_3O_4 nanoparticles that are gradually encapsulated by Ag, and it will cause a change in the color of the mixture from black to a shade that is somewhere between gray and green. The magnetic field was used to wash the separated Fe_3O_4-Ag NPs, and then they were resuspended in 20 mL of doubly deionized water.

CHARACTERIZATION OF (*Fe_3O_4-Au@ Fe_3O_4-Ag*) MNPS

To characterize the as-prepared (MNPs), optical and structural methods are used. Additionally, the powder diffraction mode of XRD (Shimadzu XRD 6000, Cu-K radiation source, angle $2\theta = 10°–80°$) is utilized. Transmission electron microscopy (TEM; Philips) was utilized in order to investigate the morphological characteristics of the MNPs. This investigation focused on the MNPs' size as well as their morphological characteristics. (Vibration Sample Magnetometer, BVH-55) was also utilized in order to carry out an analysis of the data (MNPs) [22].

MEASUREMENT TOXICITY OF (*Fe_3O_4-Au @ Fe_3O_4-Ag*) MNPS

Animal body weight examination

The age of the mice was between 6-8 weeks and their weight was 25-33 grams. The mice were divided into three groups: First group: The mice were injected with physiological phosphate solution (PBS), which represents a negative control. A second group: was injected at 1 mg/kg with Fe_3O_4-Au. A third group: was injected with 1 mg/kg of Fe_3O_4-Ag MNPs, and the three groups were left for 1, 2, 3, 4 weeks. Then, after completing the scheduled time of the experiment, the weight of a body was taken to the animal laboratory [20].

Evaluation of serum biochemical markers

At the beginning of the experiment, we drew blood from the heart of laboratory animals through a hole in the heart, and A large amount of blood. We also collected whole blood using universal tubes and It was then centrifuged at 3500 rpm and had a duration of 10 minutes in order to separate the serum. using a Biochemistry Analyzer (Chemistry Analyzer, Automated, Abbott Laboratories, and architect c4000), we also conducted a biochemical analysis in the serum in order to determine the levels of creatinine and urea in the blood for Kidney function assessment.

Tissue examination

Standard procedures were used to perform tissue analysis on kidney samples that had been repaired with formaldehyde, buffered to a pH of par (10 %), embedded in paraffin, and cut into sections measuring 5 micrometers. The sections were then stained with hematoxylin and eosin (H&E). following the application of H&E Tinted, the slides and photographs were observed and captured using an optical microscope (100X).

Statistical analysis

Data are presented as mean ± SDM, and statistical analysis is performed using t. Testing with Graph Pad Prism 9 (Graph Pad Software, USA). Differences were considered significant at

$^*p < 0.05$.

RESULTS AND DISCUSSION

Structural properties of (Fe_3O_4-Au @Fe_3O_4-Ag)

Fig. (1) shows the XRD patterns present in the particles (Fe_3O_4-Au @ Fe_3O_4-Ag). which were produced by hydrothermal treatment of spectra of Fe_3O_4 NPs with peaks corresponding to the standard XRD cubic phase spectrum of these particles (JCPDS card number 19-0629). Since the Sherrer's equation is the basis for averaging product size , the crystals, recorded as 22 nm for Fe_3O_4-Au, are nearly equation identical to TEM micrographs. The distinct peaks were clearly preserved, as shown in Fig. (1), with the exception of the peak's (Intensity and Width), which show changes due to the particle size reduction that are due to the Fe_3O_4-Ag coating NPS exhibited a particle size of 16 nm, demonstrating that the modified NPs have a structure that is very stable of its crystals. In addition, the findings demonstrated that a plating treatment alone is insufficient to bring about a growth change in the particles, which, in turn, can cause changes in their physical properties [23].

Morphological properties of (Fe_3O_4-Au @Fe_3O_4-Ag)

We examined the size and morphological properties of (Fe_3O_4-Au@Fe_3O_4-Ag) via TEM. shown in Fig. (2). Whereas, the size of the particles is about (8-22 nm and 4-16 nm) respectively, as is evidenced by the ball-like shape. It is possible that the presence of a number of aggregates on the surfaces of the Fe_3O_4-Au nanoparticles is due to surface properties such as a high energy level and a relatively large area. As for Fe_3O_4-Ag nanoparticles, it was shown It has good dispersion.

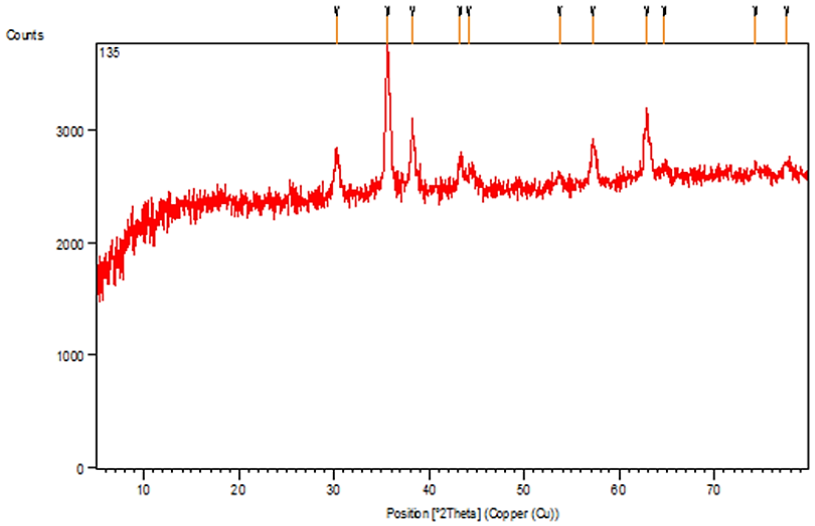

Fig. 1.1. XRD pattern of (Fe_3O_4-Au) MNPs

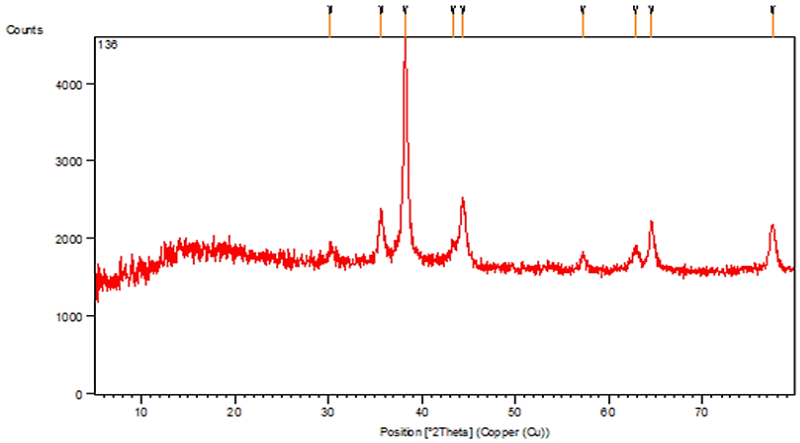

Fig. 1.2. XRD pattern of (Fe_3O_4-Ag) MNPs

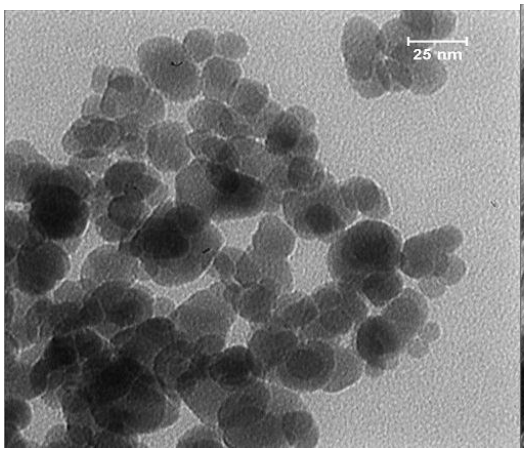

Fig. 2.1. TEM pattern of (Fe_3O_4-Au) MNPs

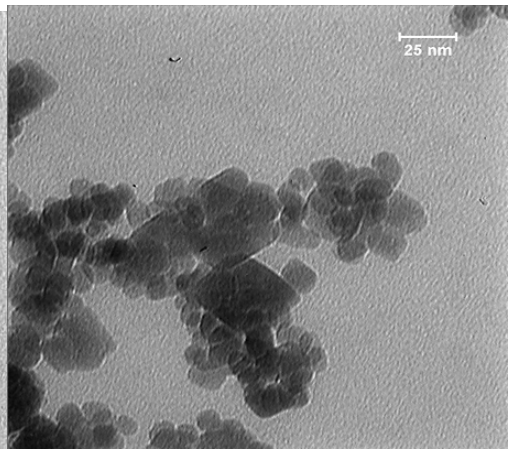

Fig. 2.2. TEM pattern of (Fe_3O_4-Ag) MNPs

Therefore, this can be attributed to the coating of nanoparticles with (Au @ Ag) Leads to reduction in size and aggregations of Fe_3O_4 nanoparticles, with improvement their dispersal [24].

Vibrating Sample Magnetometer (VSM)

Fig. (3) was shows typical magnetic curves for (Fe_3O_4-Au @ Fe_3O_4-Ag) obtained at room temperature. When such a reduction occurs after coating by (Au@Ag) nanoparticles, this indicates the reduction that occurs in the agglomeration level of the particles [24]. As the relaxation field grows larger, the amount of magnetization they possess eventually drops to a lower level. The presence of super magnetic properties in our NPs is demonstrated by the fact that neither hysteresis nor stays are observed in their magnetic behavior. The values of saturation magnetization (Ms) for samples (Fe_3O_4-Au @ Fe_3O_4-Ag) are 62.45025 and 34.44564 emu g^{-1}, respectively. where significant softening occurred in magnetic properties due to coating (Au@Ag) on Fe_3O_4. An increase in particle size was related to an increase in coercivity (Hc) and saturation magnetization (Ms) of Fe_3O_4 [25].

TOXICITY ACTIVITY (IN-VIVO) OF (*Fe_3O_4-Au @ Fe_3O_4-Ag*)MNPS

Effect of (Fe_3O_4-Au@Fe_3O_4-Ag) MNPs on Biochemical parameters

The effect of MNPs injection (Fe_3O_4-Au @ Fe_3O_4-Ag) on blood urea, and creatinine concentration are shown in Fig. (4), where the results showed that there were no statistically significant differences in urea concentration and there were no differences in creatinine In the injection serum for 1 to 4 weeks.

The organ and kidneys were also carefully examined and examined. No pathological changes were found that could be observed with the naked

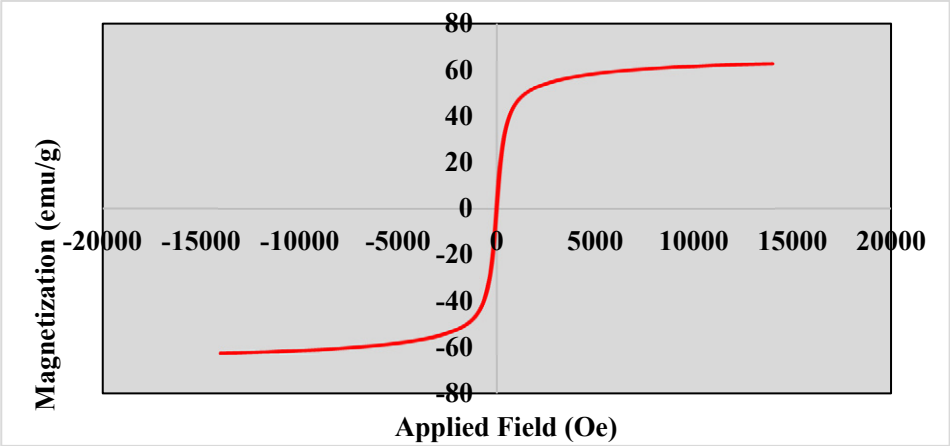

Fig. 3.1. VSM pattern of (Fe_3O_4-Au) MNPs

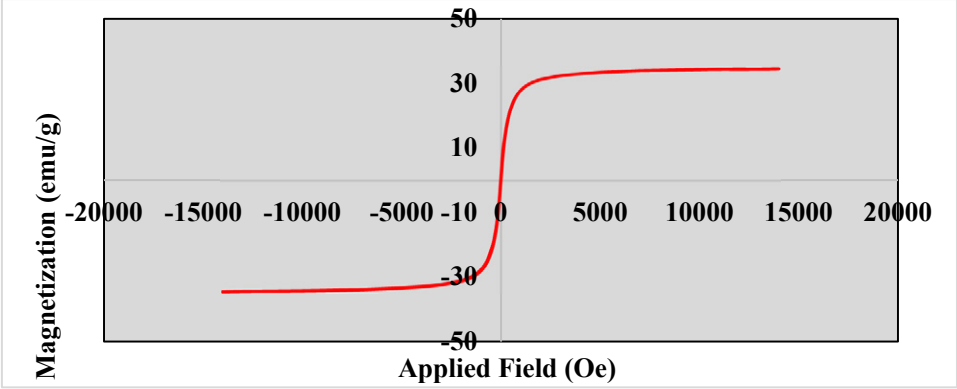

Fig. 3.2. VSM pattern of (Fe_3O_4-Ag) MNPs

eye. Also, the body weight of mice was not affected after being injected with (Fe_3O_4-Au @ Fe_3O_4-Ag) MNPs for 4 weeks, and there was no difference between the injected group and the control group, as shown in the Fig. (5).

As there was, a histopathological examination was performed in mouse tissue from the control group and treatment groups. An examination of pathological tissues was also conducted after conducting the autopsy study. Where the tissues

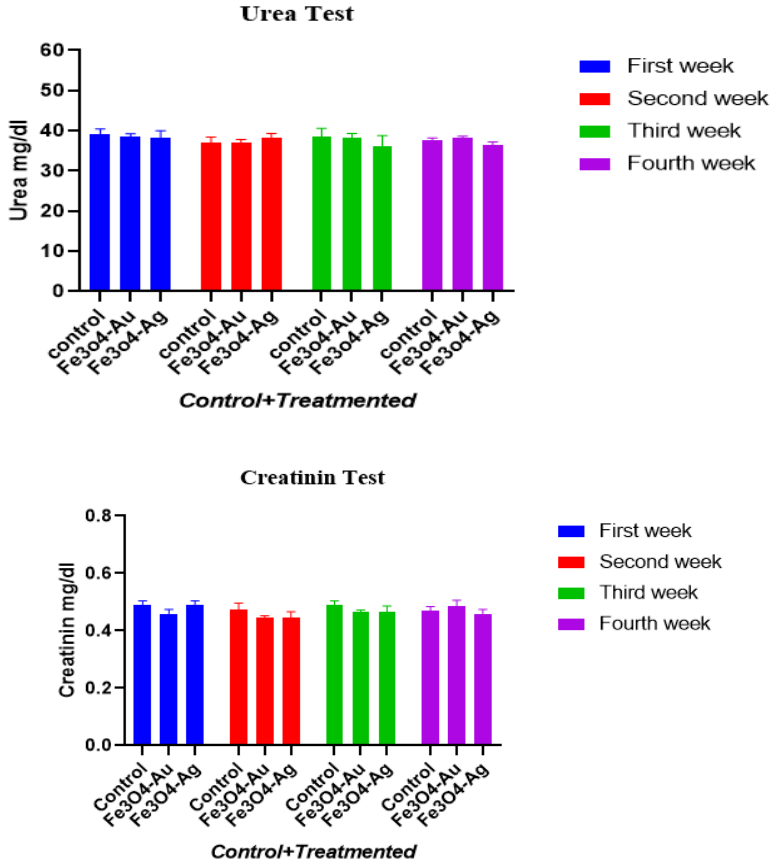

Fig. 4. Urea and creatinine level after intraperitoneal injection of (Fe_3O_4-Au@Fe_3O_4-Ag) MNPs

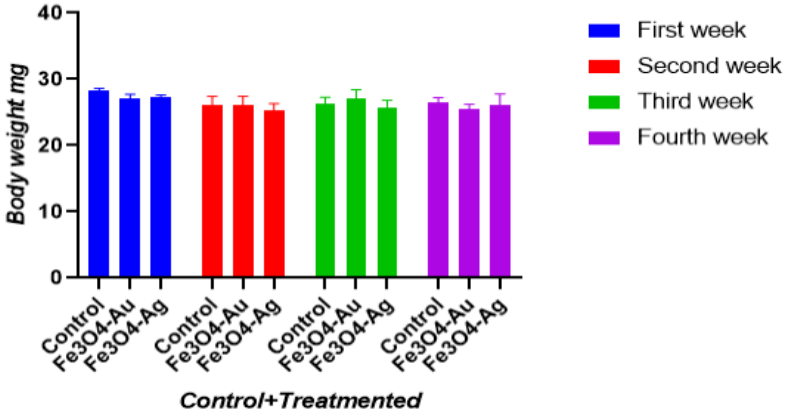

Fig. 5. Animals body weight after intraperitoneal injection of (Fe_3O_4-Au @ Fe_3O_4-Ag) MNPs

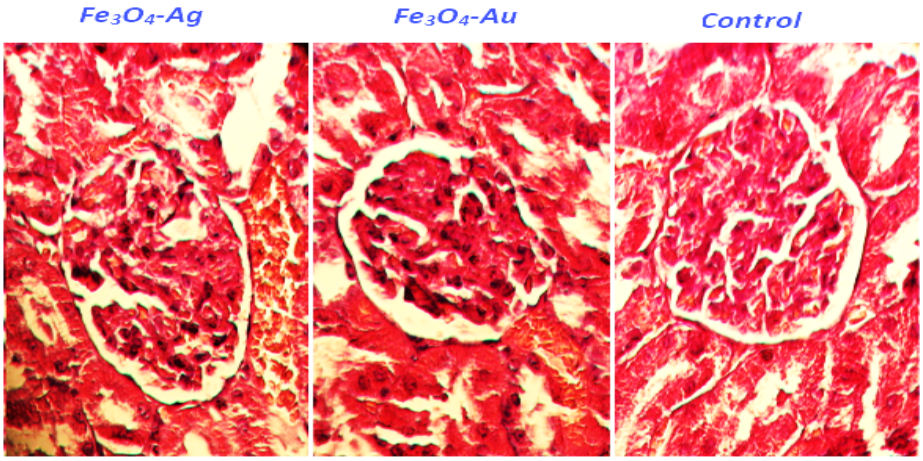

Fig. 6. Kidney histological section after intraperitoneal injection of (Fe_3O_4-Au @ Fe_3O_4-Ag) MNPs

of the control group and treatment groups did not find any significant pathological changes in the shape of the kidney ,Fig. (6). As a result, no changes appeared in the kidney nodules. Kidney tissues also appeared normal by comparing them with results with untreated animals. Also, no atrophy was seen in glomerular epithelial cells and kidney tubules in the kidneys[26-28].

Exposure to (Fe_3O_4-Au@Fe_3O_4-Ag) MNPs did not lead to any histopathological changes in treated laboratory animals. In conclusion, magnetite coated with (Fe_3O_4-Au@Fe_3O_4-Ag) are biocompatible magnetic nanoparticles, as they are considered to be less toxic. Intraperitoneal administration of (Fe_3O_4-Au@Fe_3O_4-Ag) MNPs at a dose of 1 mg/kg, there were no observations of changes in blood or histological biochemical markers for a long time after 28 days of infusion. Also, there was no difference in body weights after treatment of treated animals in (Fe_3O_4-Au @ Fe_3O_4-Ag). All of these findings are also taken into account when designing new drug delivery systems.

CONCLUSION

Through the preparation, a low agglomeration of Fe_3O_4 magnetic nanoparticles was obtained when covered with metals (gold and silver) and this leads to an increase in the ratio of the supermagnetic fracture to the magnetic fracture. The size of the particles was also reduced after Fe_3O_4 was capped by (gold and silver) and the particles were roughly spherical shape with average diameter (Fe_3O_4-Au@Fe_3O_4-Ag) (8-22 and 4-16) nm respectively. also The decrease in magnetization after plating with metals (gold and silver) is related to the reduction of particle agglomeration, with the reduction of particle size and agglomeration, as the magnetic field rotation was increased and then the magnetization decreased. Where the loss of hysteresis and survivability indicates that our nanoparticles possess superior magnetic properties. Both (Fe_3O_4-Au@Fe_3O_4-Ag) MNPs are biocompatible magnetic nanoparticles, and possess low toxicity. Intraperitoneal administration of (Fe_3O_4-Au @ Fe_3O_4-Ag) MNPs at a dose of 1 mg/kg, as there were no changes in body weight, biochemical markers, and histological section. Nanomaterial's ((Fe_3O_4-Au @ Fe_3O_4-Ag)) can also be used in all medical field like drug delivery and cancer treatment because of their small size and did not side effect.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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