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Effect of TNF-Gold Nanoparticles Combination on Kidney and Liver Parameters of Female Mice

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Abstract

Background Nanomedicine has emerged as a powerful platform for applying nanotechnology in the prevention and treating many diseases.

Objective To investigate the toxicity of designated anti-cancer drugs composed of gold nanoparticles (GNPs), tumor necrosis factor-alpha (TNF-α), and cysteine-Alanine-Leucine-Asparagine-Asparagine (CALNN) peptide on kidney and liver parameters, using animals' model.

Methods A Combination of TNF-α and CALNN peptide on the surface of GNPs were achieved depending on formation of dative covalent bond between molecules and pH of solutions, which leads to react with active groups of different molecules of nanoparticles, which characterized using ultraviolet visible spectroscopy. Moreover, their effects on kidney and liver blood variables had been examined. These blood values included measurement of the glutamic oxaloacetic transaminase, glutamic pyruvic transaminase and alkaline phosphatase, creatinine, and urea levels after intraperitoneal injection of an anti-cancer drug in female albino mice.

Results Overall, the results indicated that there was no significant change in the concentration of different biochemical values between treated and control groups.

Conclusion The results suggest that GNPs-TNF-α-CALNN combination have no harmful impact on kidney and liver organs of tested mice.

Keywords Nanomedicine, GNPs, TNF-α, CALNN peptide, drug delivery, cytotoxicity

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List of abbreviations: CALNN = Cysteine-Alanine-Leucine-Asparagine-Asparagine, GNP = Gold nanoparticles, GOT = Glutamic oxaloacetic transaminase, GPT = Glutamic pyruvic transaminase, TNF-α = Tumor necrosis factor-alpha, UV-VIS = Ultraviolet-visible

Introduction

Nanomedicine is the usage of nanotechnology in different areas of medicine, present-day nanomedicine utilizes structured nanoparticles such as dendrimers, carbon fullerenes (Buckyball's), and nanoshells to target specific tissues and organs [(1)]. Nanoparticles present particular physical and chemical features that cannot be accomplished by other materials [(2)]. One interesting example of nanoparticles is colloidal gold that exhibits many applications in biology and medicine field [(1)]. Concerning other nanoparticle materials, gold nanoparticles (GNPs) have been used broadly in a different area of nanomedicine [(3)]. In the last two decades, highly advances in the field of nanoparticles-based therapeutically agents and in diagnostic tools for varying diseases like cancer, asthma, allergy, diabetes, infections, and a lot more were achieved [(4,5)]. These therapeutic agents could be more effective

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when injected in an appropriate route of administration, lowering the toxicity of drugs, and increase the lifetime of the product, as a result, this will reduce health care costs [6]. Development of cancer nanotechnology enables and motivates the growing of securer yet more effective therapeutic agents and diagnostic methods for cancer therapy [7,8]. One of the important issues in nanoparticles-based studies is to achieve an efficient drug delivery system targeting to tumors as well monitoring the drug bioavailability throughout the body and accumulation within tumors [9,10]. GNPs have special characteristics over other types of nanoparticles that made them dedicated to using in different aspect of medicine and cancer research due to their size, shape and surface area, which can be easily customized, besides several lines of evidence have investigated the biocompatibility of GNPs and the minimal effect of toxicity [3,11].

Recently, CALNN peptide had been used in the treatment of different types of diseases, it is a pentapeptide composed of 5 amino acids, include Cys-Ala-Leu-Asn-Asn (CALNN) [12]. The use of therapeutic peptides over proteins relying on many characteristics including the size of a peptide, and the ability to penetrate the cell membranes. Besides peptides have increased activity, specificity and affinity; and biological and chemical diversity of therapeutic the agents [13]. Several lines of evidence emphasized the use of tumor necrosis factor-alpha (TNF-α) as anti-cancer therapy since it can affect both the cells and vasculature of the tumor and result in a reduction of the tumor volume [14,15]. However, dose-limiting toxicity is considered as the main problem for the systemic administration of TNF-α [16,17]. Therefore, there is a need for selective tumor delivery of TNF-α to reduce systemic toxicity.

The objective of this research is to determine whether the designated nanoparticles delivering system have any side effect or toxicity on the function of the kidney and liver of female albino mice after repeated intraperitoneal injections.

Methods

Characterization of the combination of GNPs, TNF-α (obtained from Sigma Aldrich, USA), and CALNN peptide (obtained from the University of Ioannina, Greece) by using ultraviolet-visible (UV-VIS) spectrum analysis.

Animals

Female healthy mice (8-10) weeks old, (15-25 g) weight housed that has been brought from Iraqi Center for Drug Monitoring, Baghdad, and kept in Iraqi Center for Cancer and Medical Genetic Research (ICCMGR) animal house, with controlled conditions of temperature (23±5°C) and relevant humidity. Animals were kept in partitioned cages and supplied with wood dust and tested for any accidental infection before starting the experiment [18].

The animals were distributed randomly into 3 treatment groups besides one control group, each group consisting of 3 mice. The concentration of compounds used in the treatment as followed 500 µg/Kg for GNPs and CALNN and 0.5 µg/Kg for TNF-α, the compounds were injected intraperitoneally every 3 days for 1, 2, 3 and 4 weeks and animals were sacrificed at the end of the experimental period as follows first, second, third and fourth weeks, the weight of mice was measured by using digit balance before each drug administration, the activity of mice also monitored during the experimental period. The first group was administrated with GNPs only, whereas GNPs-TNF-α was delivered intraperitoneally, as for the third group the animals were injected with a combination of GNPs-TNF-α-CALNN. For biochemical testing, the blood samples were collected using heart puncture, and then blood samples were centrifuged for about 10 minutes at 4000 rpm, serum aspirated in clean tubes, and kept at -20°C for later use.

Statistical analysis

Graph Pad Prism 7.0 software was done to analyses the results by using the unpaired T-test method, P-value of < 0.05 considered to be significant [19].

Results

Characterization

The combination of GNPs-TNF-α and GNPs-TNF-α-CALNN was confirmed by UV-VIS spectroscopy as showed in figure (1). The top peak of GNPs could be noticed at 520 nm, whereas for TNF-α that attached to GNPs, the top band was shifted and appear very clear bands. However, when GNPs-TNF-α binding to CALNN peptide the top band would be shifted more to be at 680 nm.

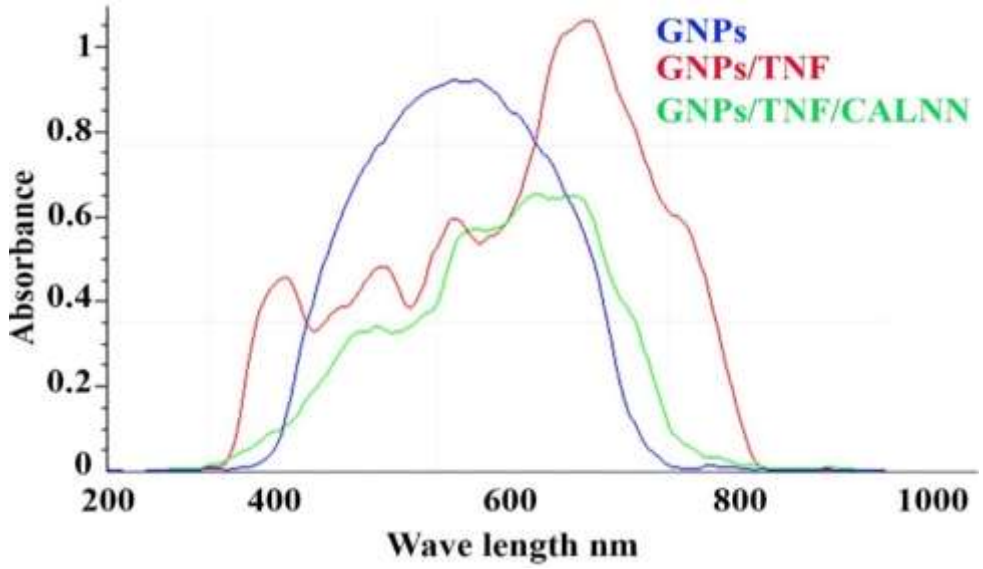

Figure 1. Ultraviolet-visible spectroscopy of GNPs, TNF-α loaded on GNPs and GNPs-TNF-α-CALNN

Effect of drug delivery system on the weight of experimental animals

Evaluation of the body weight of experimental animals throughout the experimental period after intraperitoneal injection with GNPs, GNPs-TNF-α, GNPs-TNF-α-CALNN compounds was achieved by using electric balance, the body weight value was recorded for each group and results of body weight appeared to be unaffected by different types of treatment (Figure 2).

Effect of drug delivery system on biochemical parameters of kidney and liver of experimental animals

To investigate the effect of these compounds on kidney and liver function, urea, creatinine, glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT) and alkaline phosphatase concentration were measured and compared the data with a normal value of control groups [20,21]. The results exhibited no significant differences between treated and control groups as set out in figures 3 and 4.

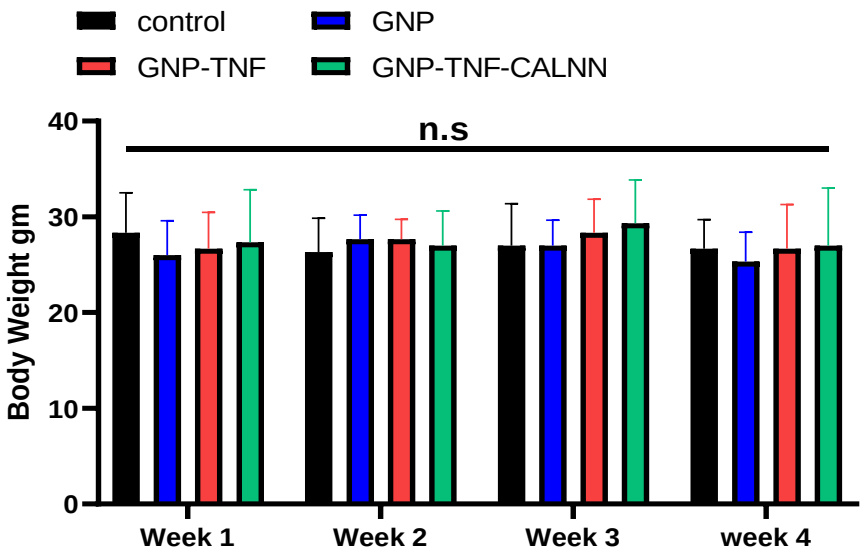

Figure 2. Effect of GNPs, GNPs-TNF-α and GNPs-TNF-α-CALNN in animal body weight

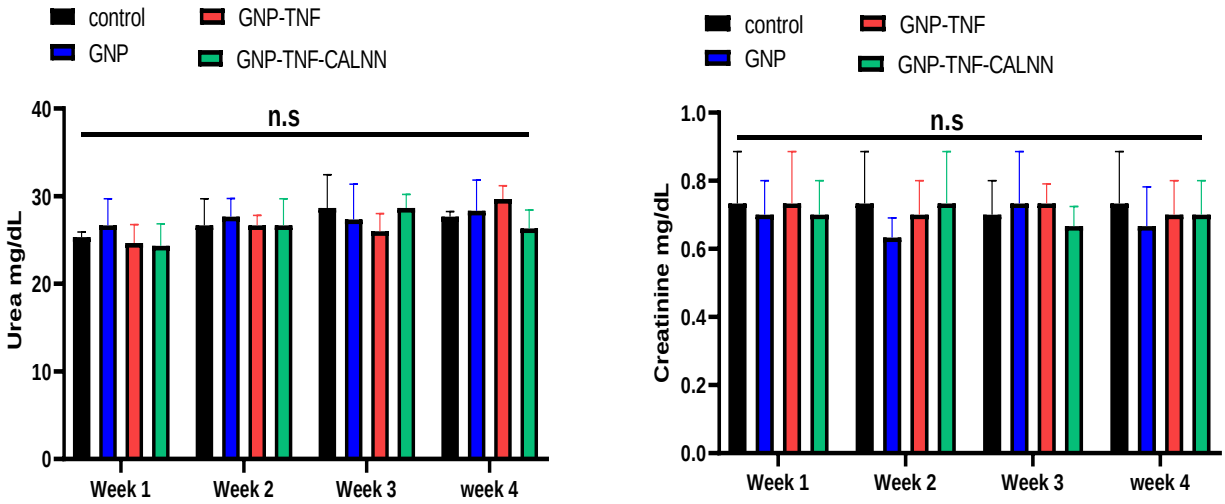

Figure 3. Effect of GNPs, GNPs-TNF-α, and GNPs-TNF-α-CALNN treatment group in urea and creatinine concentration

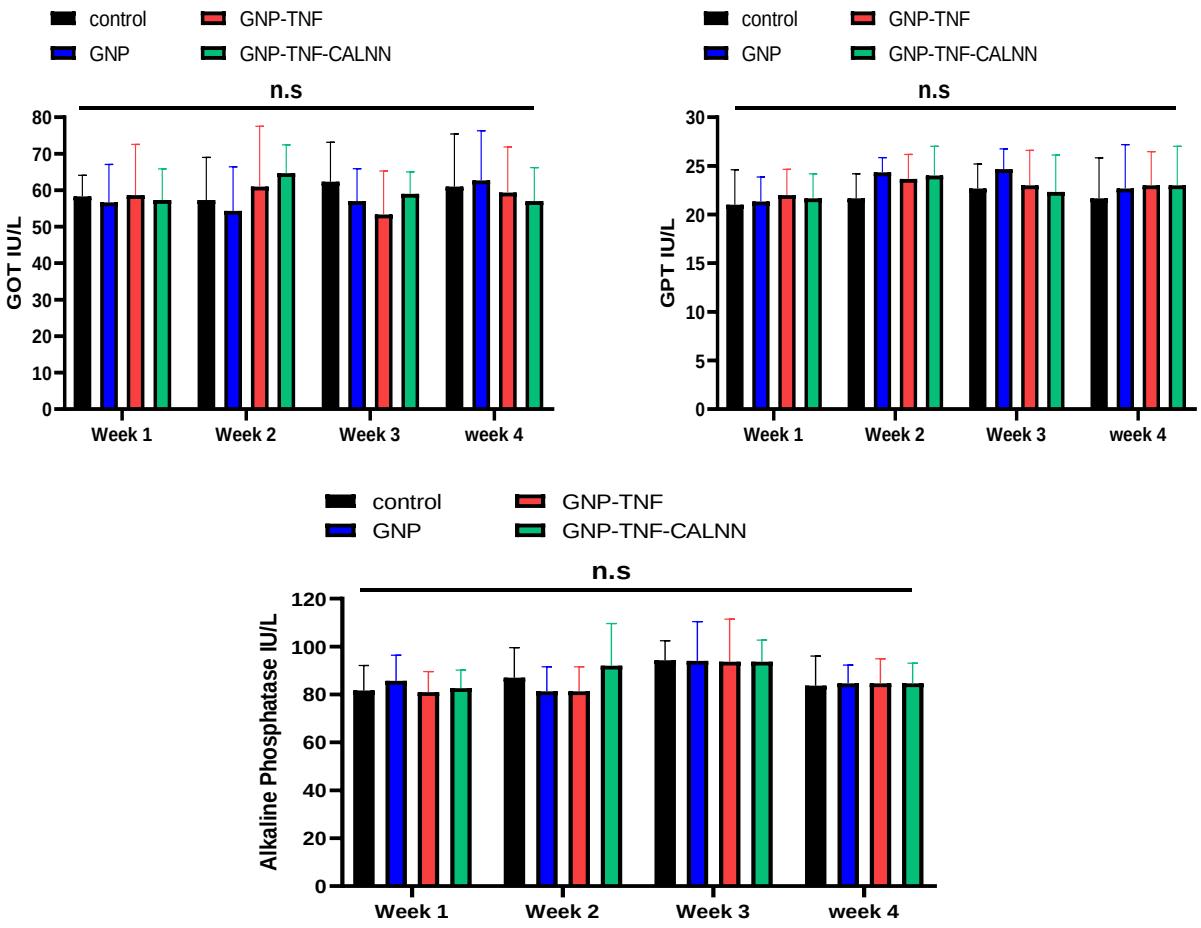

Figure 4. Effect of GNPs, GNPs-TNF-α, and GNPs-TNF-α-CALNN treatment group in GOT, GPT, and Alkaline Phosphatase

Discussion

Data suggested that healthy animal does not exhibit any cytotoxic effect after received the treatment drugs intraperitoneally, also their biological parameters were normal. The body weight for three different groups showed non-significant differences in compared to control group. Also, the present results corroborate the idea of Zang et al. [22], who suggested that particles used in his experiment were absorbed by both hepatocytes and Kupffer cells and secreted in two different periods, as for hepatocytes that engulf particles within first 2-6 hours and secreted through hepatobiliary pathway during the first 24 hours, while Kupffer cells secreted the ingested particles lately (after 24 hours) by an unknown mechanism. These results seem to be consistence with Renaud et al. [23] who suggested two phases explained as an early phase and late phase of gold particles excreted from the liver, the clearance mechanism lay on the earlier circulation of gold nanoparticles with parenchymal and nonparenchymal cells and does not exhibit a cytotoxic effect on the liver. A comparison of the findings with those of other studies confirms that GNPs loaded with TNF-α and CALNN peptide do not have any cytotoxic effect on the liver and kidney.

In conclusions, this study has argued the effect of designated drug delivery compounds on some of the essential biochemical parameters of the kidney and liver. The following conclusions can be drawn from the present study was injected GNP, GNP-TNF-α, and the combination of GNP- TNF-α-CALNN don't show a toxic effect on female albino mice after 1, 2, 3 and 4 weeks of intraperitoneal injections.

Together these results provide important insights into the fact that using these compounds together as a drug-delivering system does not affect kidney tissues and function and could be used as an anti-cancer drug system safely, without affecting normal tissues.

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Author contribution
Dr. Abood: Performed the experiments and writing the manuscript. Dr. Kadhim: Supervised the study and made the final revision of the article. Dr. Jabir: Designed the study and carried out the data analysis.

Conflict of interest
No potential conflict of interest was reported by the authors.

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