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Original Article

Hepato-Renal Dysfunctions Induced by Gold Nanoparticles and Preservative Efficacy of Black Seed Oil

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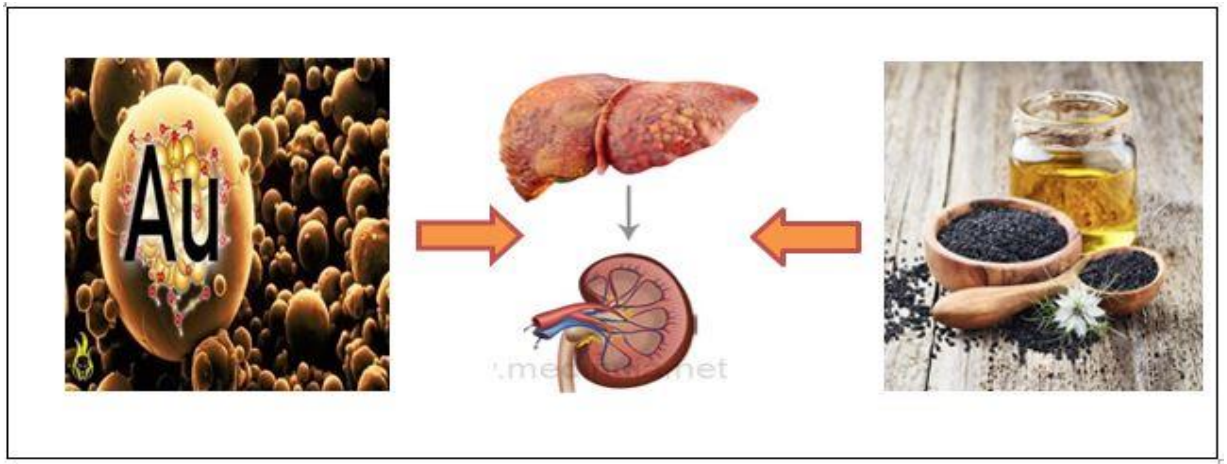
A B S T R A C T

Gold nanoparticles (GNPs) represent the most important applications of nanotechnology in fields of medicine. The study aimed at clarifying their toxic effect, especially upon biochemical parameters related to liver and kidney functions of lab animals. Twenty-four healthy rats were distributed on 4 groups, each containing 6 rats. Control group included rats without any treatment, while GNPs group of mice were under intoxication with gold nanoparticles at a dosage of 50 µl/day for 7 days. As for the GNPs + BS group, intoxicated rats with GNPs were given oil of black seed at a dosage of 10 ml / kg. Finally, BS group included rats were under treatment of 1 ml/ kg of black seed oil. Serum levels of hepato-renal parameters including alanine amino transferase, aspartate amino transferase, alkaline phosphatase, blood urea, creatinine, and uric acid, were measured to detect impaired liver and kidneys functions. Rats treated with GNPs indicated a substantial ($P < 0.05$) increase in all these biomarkers levels contrasted to the group of control. Then, co-administration of black seed oil together with GNPs had a significant effect on reducing hepatorenal functions disorders. Thus, from these results, it can be concluded that the black seed oil has shown a defensive effect against the disturbances caused by GNPs in the liver and kidney functions of rats.

G R A P H I C A L   A B S T R A C T



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Introduction

Application of nanotechnology in medicine may revolutionize healthcare [1]. Noble nanoparticles such as gold nanoparticles (GNPs) are a promising emerging trend for the design of bioengineered materials that are used in the diagnosis and control of critical diseases [2]. The increasing employment of nanomaterials (NMs) rose up concerns about their potential risks. Nanotoxicology is an emerging scientific branch concerned with the study of the potentially harmful nanoparticles effects and related parameters affecting the cytotoxicity of nanomaterial [3]. Several studies have reported that gold nanoparticles accumulate in various organs of experimental rats, including the liver and kidneys [4,5]. In another context, previous studies in laboratory animals have concluded that different types of NMs produce toxic effects in different organs depending on dose concentrations and duration of exposure [6,7]. Dimensions and surface area of NM are factors that increase the production of reactive oxygen species (ROS), which may lead to impaired function in the liver and kidneys [8]. Herbs from ancient times until now occupy an important space in medicine, especially treatment and prevention in many developing countries due to the possibility of agriculture and the human body's acceptance of them with the least side effects [9]. Black seed (Nigella sativa), a blossoming herb growing in some countries of the Middle East, is considered one of the traditional herbal medicines that has increased in interest today in the world. It has a variety of beneficial properties [10], among which it reduces a lot of toxicity caused by drugs and chemicals [11]. The defending effects of such plant towards toxic chemicals in various organs such as kidneys and liver have been determined by previous research [12,13]. Thymoquinone (TQ) could be the key active material in the essential oil at up to 50% [14]. Here, in such a study, various biochemical parameters were tested to assess clinicopathological profile of impaired liver and kidney functions in rats poisoned with GNPs and to elucidate the potential protective benefits of black seed oil through its impacts upon toxicity reduction and upon biochemical improvements of hepato-renal functions

Material and methods

Chemicals

Gold nanoparticles suspension liquid was taken from Nanoshell LLC Company (USA), purity: 99.9%, APS: 5 nm, molecular weight: 196.97 g/mol, density: 19.32 g/cm^3, pH: 5-7. As for the black seed oil supplement, it was from Harper Research LLC of Vine Nutrition (USA). It was taken orally 10 ml / kg daily by gavage tube throughout the experimental days [15].

Animals and study design

24 male albino rats with ~160-200 g weight were attained out of the laboratory of animals. The sample animals in this study were placed in designated cages in an air-conditioned room maintained on a light/dark cycle for 12 hours, and accessed to water and diet ad libitum. Rats were adapted for fortnights to lab conditions before initiating this experiment. They were distributed into four groups, each consisting of six rats as shown in Table 1.

Table 1: Groups of the experiment

Groups	Experimental Design
CON	Healthy rats as control
GNPs	50 µl (0.25 ml/kg) of GNPs were managed to rats intraperitoneally, for 7 days [16]
GNPs + BS	Intoxicated rats with GNPs were under treatment with black seed oil at a dose 10 ml / kg, for 7 days
BS	Animals were dosed with black seed oil for 7 days

After 24 hours from the end of the last treatment dose, the rats were dissected and samples of their blood were collected by cardiac hole without using of anticoagulants to perform biochemical analyzes. Whereas, liver and kidney functions parameters were standardized by diagnostic kits (Roche) into an automated chemical instrument.

Liver function biomarkers

Serum levels of liver functional markers were determined by measuring the levels of the following serum enzymes: AST, ALT, and ALP stand for alkaline phosphatase, alanine aminotransferase, and alkaline phosphatase, respectively (Figure 1).

Kidney function biomarkers

To evaluate kidney function, blood urea (BU), creatinine (CR) and uric acid (UR) levels were determined using an automated biochemical analyzer.

Ethical issues

This experimental study was carried out in accordance with the regulations of the research ethics committee of Iraqi technical universities ethical guidelines for the use of animals in research. Animal experiments were performed according to protocols approved by the US National Institutes of Health (NIH, 1978).

Statistical analysis

IBM-SPSS version 26 was used to analyze all the statistics, and expressed as mean ± standard deviation (DS). One-way ANOVA was applied for the different groups followed by Duncan test. P-value was considered a statistically significant difference if it was less than 0.05.

Results and Discussion

Figure 1 presents the levels of serum related to functional markers of liver for the various groups of rats involved in this study. Rats under treatment with GNPs were significantly ($P < 0.05$) increased in ALT (122.06±3.17), AST (188.81 ±4.45), and ALP (411.32±8.55), when compared with the control groups (90.32±3.44; 120.98±3.71; 312.84±9.28 respectively). However, rats under treatment with GNPs and BS showed a significant decrease in these hepatic biomarkers (100.04±3.78; 146.52±4.44; 347.35±7.79, respectively) in comparison to the ones under treatment of GNP. In addition, no significant difference among control and BS rats treated alone were noticed. Figure 2 shows the levels of biochemical parameters related to the functional tests of the kidneys. There is a significant ($P < 0.05$) increase in serum BU (29.66±0.45), CR (0.60±0.03) and UR (1.67 ±0.10) levels in the GNPs groups compared with healthy control rats (21.51±0.44; 0.44±0.02; 1.02±0.04, respectively). While rats treated with GNPs and BS showed a significant reduce in levels of renal biomarkers compared to GNP-treated rats.

Nanoparticles (NPs) are considered more toxic than microparticles because of their high ability to penetrate living cells, move inside the body and have a clear effect on the functions of major organs, aided by their small size and high surface area [17]. However, GNPs with a size of up to 6 nm were found in the cell nucleus. Also, the size of 1.4 nm GNPs was found to be 60 times more toxic than that of 15 nm GNPs [18]. NPs deposited in organs generates reactive oxygen species (ROS) that induce oxidative stress and make cells disqualified to perform the physiological functions that regulate redox. This excessive ROS production leads to several problems, including protein modifications, DNA damage, and activation of inflammatory signals that lead to apoptosis, necrosis, and genotoxic effects [19,20]. Liver is the main filtering organ in the mammalian body, which acts alongside the circulatory system to capture circulating nanoparticles [21]. A substantial increase in serum hepatic enzymes ALT, ALP and AST indicates liver cell damage or breakage [22]. Increased or altered levels of these markers are associated with leakage of hepatocyte content from the liver cell membrane because these nanoparticles have the ability to cause damage to hepatocytes by oxidative stress or/and injury to organelles due to their size and structure that causes serious cytotoxicity [23]. This may explain the instability of liver function caused by MNPs. On the other hand, the kidneys cleanse the NPs absorbed into the blood. Levels of blood urea, creatinine, and uric acid are treated as key plasma markers to assess the function of the kidney. It should be noted that renal function nephrotoxicity is due to elevation in levels of these biomarkers [24]. Black seed is used as an adjunct therapy along with modern medicine to counteract the adverse effects, and many studies have been conducted on laboratory animals to evaluate the pharmacological efficacy of BS and its oil. Some of them have included studies of its efficacy in manifestations that are ostensive toxic related to the employment of certain common medications. It restores nephrotoxicity and hepatotoxicity induced by these substances. Among the mechanisms used by BS to reduce toxicity are the following: Anti-inflammatory, antioxidant, restoration of antioxidant defense systems, scavenging of free radicals, enhancement of troubled levels of biochemical markers, regulatory effects on gene expression and inhibition of apoptosis, and several signaling conduits [25,26]. It has traditionally been used to treat liver diseases and is referred to as a liver tonic. Also, BS acts as a diuretic and anti-urinary retention. Thymoquinone is the active ingredient that possesses the most therapeutic effects. There are many reports of the use of thymoquinone to regulate normal kidney and liver functions [27,28]. In addition, researchers have indicated a decrease in hepatorenal damage in animals under TQ-treatment, regardless of the core etiology [29-31]. Resultantly, of TQ administration, nearly all researchers have agreed on enhancement in hepato-renal functions with decreased liver and kidneys parameters, because such results demonstrate that TQ has some interactions with markers of oxidative stress to enhance the antioxidant system [32]. In addition, TQ has improved the histopathological changes of the kidneys induced by CLP, nephrotoxic factors, and diabetic nephropathy [33]. This is found in line with the findings of this study, proving that GNPs caused an increase in the levels of renal and hepatic enzymes, but a significant decrease occurred in them when combined with black seed oil, which indicated the improvement of liver and kidneys functions.

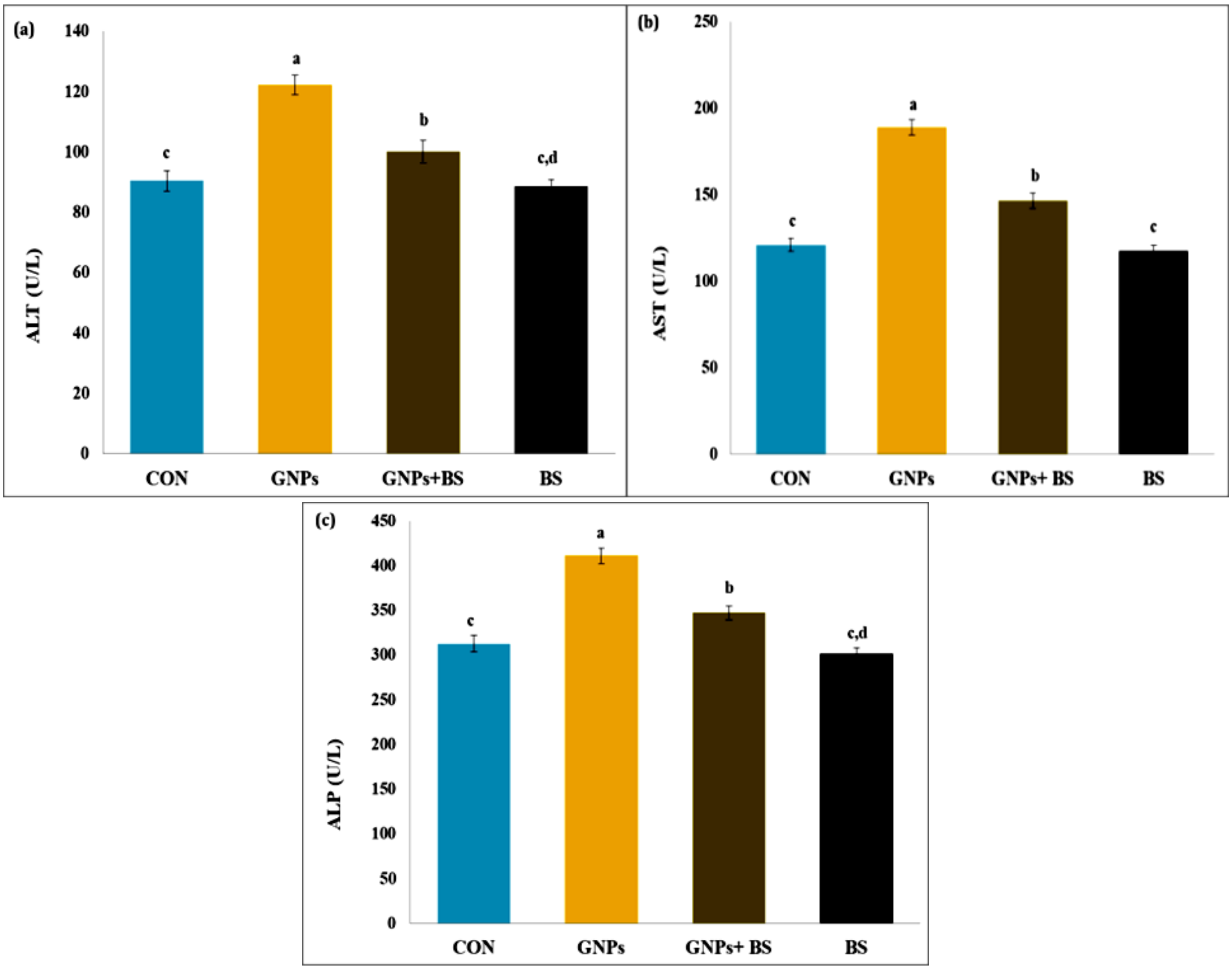

Figure 1: Levels of function parameters of liver: a) ALT, b) AST, c) ALP, for experimental groups. Data were indicated as mean ± SD. Different superscripts indicate significant intra-column differences ($p < 0.05$), Test = ANOVA, post hoc = Duncan

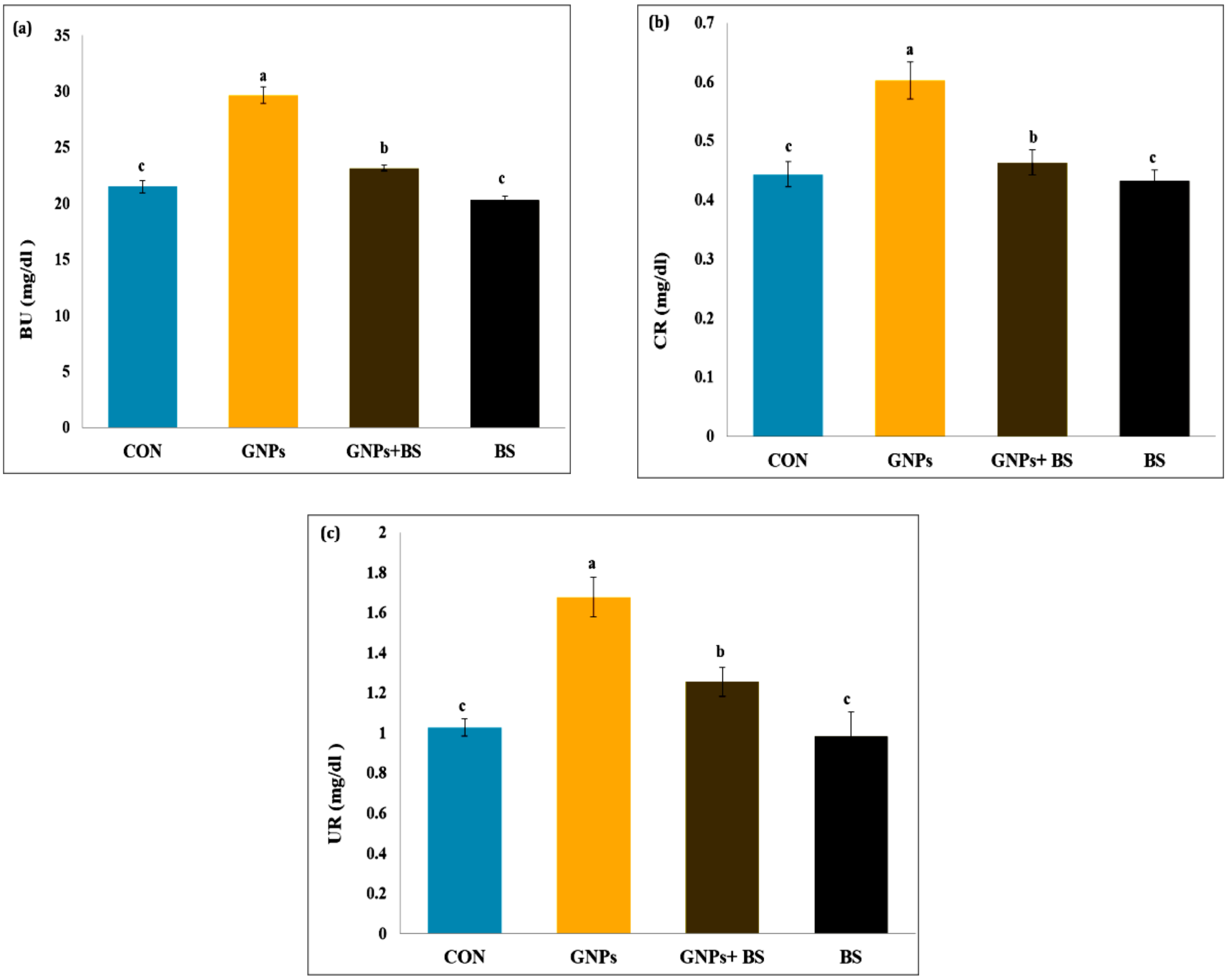

Figure 2: Levels of function parameters of kidneys: a) BU, b) CR, c) UR, for experimental groups. Data were indicated as mean ± SD. Different superscripts indicate significant intra-column differences ($p < 0.05$), Test = ANOVA, post hoc = Duncan

Conclusion

Because the study and understanding of nanotoxicity is a necessity to ensure the safety of products used NPs, especially in the medical field. Therefore, many advanced research must be conducted to create and design NPs with minimal or even no negative impact. According to the results of this experiment, black seed oil reduced the toxicity of gold nanoparticles by re-regulating the disturbed levels of biochemical enzymes in the serum and improving hepato-renal functions.

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