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Appraisal the toxicity of CaO and Gold Nanoparticles in Wistar rats: A systematic review

Shurooq Wesam Al-Shaibani [1, *], Warood Kream Alaarage [1], Maha Hatem Abdul Wahid [1] and Abtesam Imhemed Aljdaimi [2]

[1] *Department of Basic Science, Faculty of Dentistry, University of Kufa, Al-Najaf, Iraq.*
[2] *College of Dentistry and Oral Surgery, Alasmarya University.*

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Abstract

Nanotechnology is a new science and these risks are not realistically defined or observed at present. Among these risks is that particles with a diameter of 300 nanometers or smaller can with no trouble penetrate the human body also penetrate cells, as well as that particles with a diameter of 70 nanometers or smaller can easily enter the nucleus of the cell. It is possible to imagine the potential danger to the body, as an interaction may occur between nanoparticles. Because of the small size of nanoparticles, masks and even protective masks of all types are not useful for protection against them, as these particles can penetrate them. The actual impact of nanoparticles on liver and kidney function otherwise male fertility and toxicity is assessed afterward a careful investigation of the obtainable literature. The chief role reviews animal patterns to comprehend the biomarkers related to the function of the liver and kidneys, also testis function of nanoparticles. Our principal outcomes put forward that nanoparticles are in general capable to reach the liver, kidneys, and the testicle in minor quantities where they persevere for more than a few months, nevertheless of the route of exposure. Notable, the majority of nanoparticles have little shortest toxicity to liver, kidneys, and the testis. Research conducted on mice and laboratory animals has shown that nanoparticles, after entering their bodies, tend to migrate and localize in the liver, kidney and that these particles can penetrate to reproductive system, and nanoparticles can also localize in other organs.

Keywords: Nanotechnology; Toxicity; Silver; Systematic Review

1. Introduction

Nanotechnology has advanced quickly in the previous several years in a variety of areas of human life, like agriculture, industry, food, medical, cosmetics, and more [1–4]. Although nanomaterials are widely used, there is a severe dearth of knowledge regarding the influences of nanoparticles (NPs) on the environment and human health [5]. NPs are substances or particles with a size ranging from 1 to 100 nanometers [6,7]. The primary characteristics of NPs are their size, electronic configurations related to their structure, and their exceptionally great surface-to-volume ratio in comparison to greater part substances [8]. Because of their nanoscale size, NPs can pass throughout cells as well as reach other regions of the body or pass through cell membranes to insert cells, primarily through the respiratory system [9]. As a result, the area of nanotoxicology still lacks the knowledge and explanations required to do accurate risk assessment [10].

Numerous metal oxide NPs, including molybdenum disulfide (MoS_2) [11,12], titanium dioxide (TiO_2) [13,14], silver [15], and calcium-based compounds [16,17], have been produced and published in the literature. The ability of calcium-based NPs to discharge calcium ions, which are fundamental components of human bones and teeth [18,19] and are considered to be an essential mineral for all living things [20,21], has led to the recommendation of these NPs in a number of medical and dental studies [22].

* Corresponding author: Shurooq Wesam Al-Shaibani

Calcium oxide (CaO) Applications include tissue engineering, the petroleum industry, the cement industry, the manufacturing of biodiesel, biosensors, electric lighting, and power generation [19]. CaO-NPs were prepared using a variety of physical techniques. Although CaO-NPs can be created in a variety of ways [23], their most common forms are commercially made and conventionally prepared [24]. These particles exhibit antibacterial capabilities against tested organisms such Staphylococcus epidermidis, Pseudomonas aeruginosa, in addition to Candida tropicalis, and are widely utilized in drug delivery [25]. Research has shown that animals exposed to excessive dosages of Ca-NPs may experience toxic effects, especially in the liver and kidneys. These organs may experience inflammation and cell damage as a result of the buildup of Ca-NPs, which would affect the functionality of the organs [26].

Due to their special qualities, which include biocompatibility, great surface reactivity, confrontation to oxidation, flexibility in functionalization, and a broad spectrum of delivery targets, gold-nanoparticles (GNPs) have exciting therapeutic potential [27–31]. In recent years, GNPs have been widely used in Nano medicine, drug transport, diagnosis, radiotherapy, gene and photo thermal therapy, bio sensing, then diagnosis, and therapy of cancer [32,33]. They have also been applied extensively in medicine, diagnostics, catalysis, and sensors [34], and various industries like beverages, toothpaste, and vehicles [35]. Nevertheless, the rising use of GNPs has caused an accumulation of them in tissue cells, raising the risk of its toxic effects on humans. When assessing GNPs' possible effects on human health, it is crucial to comprehend their reproductive toxicity [36–40]. The physical properties of GNPs, including their shape, size, surface composition, and chemistry (including coating) [41], as well as their production methods, length of exposure, dose, and mode of administration, all influence their toxicity and dispersion [42]. Owing to the different GNPs modifications, surface functional attachments, Nano sphere shape, and diameter size, there are varying reports regarding the degree of toxicity associated with these particles [43,44]. According to Abdelhalim and Jarrar's 2011 researches, exposure length and size affect how much GNPs bioaccumulation in a variety of rat tissues, including the kidney, lung, liver, and heart. Prior research has not adequately verified the effects of GNPs size and exposure length on rat liver and kidney function in vivo [45–48].

Thus, the present manuscript aims to compare the toxic validities of CaO-NPs and GNPs in main systems, especially the renal and hepatic systems. As well as the extent of their effects on the fertility of Wistar rats.

2. Materials and Methods

Despite the large number of studies conducted on nanomaterials of various types (mercury, silver, cobalt, gold, nickel, copper, and calcium), these studies still do not provide sufficient information to ensure the safety of these materials for use in the future in a variety of fields, including industrial, medical, and other areas of life that have advanced recently. By comparing the effects of nanomaterials on the fertility of laboratory rats, and their effects on the liver and kidneys, the researchers aimed to determine the extent of nanomaterials' significance and determine which ones are the least toxic.

(12) research papers were collected, including (6) Nano-gold and (6) Nanoscale CaO, where some parameters were studied, such as (ALT, ALP, Glucose, Lipid Profile, Uric acid, Urea, Creatinine, Testosterone hormone, histology changes in testis, kidney tissues).

In this study, a comparison was made between the results for the above criteria.

3. Results

All the data that the researchers reached in their results are in Table (1):

Table 1 Summary of studies exploring virtual toxicity of NPs, including: (ALT, ALP, Glucose, Lipid Profile, Uric acid, Urea, Creatinine, Testosterone hormone), histology changes in testis, kidney tissues

Publication	**Animal Model** **Route and Duration of Exposure**	**Particle Model** **Particle concentration** **Particle Measurement Method**	**Results**
Mohammad reza Behnammorshedi et al (2015) [49]	Male Rat. intraperitoneal injection of 0.5 cc	GNPs 100, 50, 25 ppm	(The mean level of Testosterone was found to be decreased) with an increased dose of NPs.

	GNPs 10 days of treatment	Transmission electron microscope (TEM).	
Bekhti Sari Fadia et al (2022) [6]	Male Wistar Rat caudal injection Fifteen days	GNPs (25, 50, 100, as well as 250) mg/kg of body weight 1- TEM and 2-UV–vis spectroscopy results of GNPs. 3- Dynamic light spectra of the GNPs	Urea as well as uric acid was increased in all rats treated with GNPs.
Doaa Mansour et al (2022) [50]	male rats intramuscular (i.m) injected for (5) weeks followed by (3) weeks washout period	GNPs 50 nm and10 nm GNPs transmission electron microscopy (TEM)	The injection of a single dose of (50 or 10) nm GNPs had no significant effect on serum testosterone level days 3 and 7. The injection of (single or repeated) doses of 10nm GNPs significantly increased serum testosterone level on Day 60 post-treatment.
Sahar H Orabi et al (2020) [51]	male albino rats intramuscular (i.m) injection for (5) weeks, followed by (3) weeks washout period for all groups	GNPs 50 nm and10 nm GNPs	The results show higher serum (ALT, AST, ALP, urea, creatinine, glucose, and different lipid profiles) and also decreased (HDL) levels.
Mohamed Anwar et al (2013) [52]	Male Wistar rat intraperitoneally managed in rats for exposure duration of (3) days.	GNPs The 50 Ml of 10 and 50 nm GNPs	The (AST) levels increased in (10 and 50) nm GNPs. The (GGT, ALT as well as ALP) levels decreased in (10 and 50) nm GNPs. Also the levels of (UREA and CREA) levels increased in a non-significant manner after the administration of (10 and 50) nm GNPs.
Ying Liu et al (2020) [53]	Male Mice intravenously injected for 14 consecutive days	GNPs 5 nm transmission electron microscope (TEM)	GNPs (5 nm) were able to be assumed into the (endosomes/lysosomes) of TM3 -Leydig cells, encourage the formation of auto phagosomes, then increase the making of (reactive oxygen species), and disrupt the cell cycle in synthesis (S phase), resulting in concentration-dependent cytotoxicity and DNA damage. Interestingly, GNPs significantly reduced testosterone production One week after withdrawal, the level of plasma testosterone in the (0.5) mg/kg GNPs group was significantly reduced
Shurooq Wesam Al-Shaibani et al (2019) [54]	male Wister Rats orally managed for 60 days	CaO-NPs (25,50and100) mg/kg from the body weight	The cholesterol values were significantly decreased in both experimental groups (25 and 100) mg/kg as compared with the control group, while the experimental group (50mg/kg) was a significant elevation. There was a significant decrease in triglyceride (TG) and very low – density lipoprotein (VLDL)

		X-ray diffractometer, spectrophotometer	values from the experimental groups compared with control. High-density lipoprotein (HDL) was significantly increased in the experimental group (50mg/kg), but no significant in both groups (25, 100 mg/kg) compared with the control. Low-density lipoprotein (LDL) was significantly decreased in the experimental groups (100mg/kg), but no significant in both groups (25, 50mg/kg) compared with control.
Shurooq Wesam Al-Shaibani(2018) [55]	male Wister Rats orally managed for 10 days	CaO-NPs (25,50and100) mg/kg from the body weight X-ray diffractometer, spectrophotometer	The levels of (glucose, blood urea nitrogen (BUN), the blood urea, the uric acid, and the creatinine were calculated. The changes in (the serum particular considerations) indicated that the kidneys were – significantly- affected in both the experimental groups. The changes among the levels of the total glucose, the blood urea nitrogen, uric acid, and creatinine) which that indicate renal damage in treated male rats.
Shurooq Wesam Al-Shaibani et al (2019) [56]	male Wister Rats orally managed for 10 days	CaO-NPs (25,50and100) mg/kg from the body weight X-ray diffractometer, spectrophotometer	The (AST as well as ALP) levels varied in the serum of both CaO-NPs treated groups. The levels of AST were significantly increased in (50 and 100) (mg/ kg) of CaO-NPs treated group. While the levels of ALT were no changes in both the experimental groups.
Khawla A. Kasar1 et al (2021) [57]	male Wister Rats orally managed for 10 days	CaO-NPs (25,50and100) mg/kg from the body weight X-ray diffractometer, spectrophotometer	The necrosis of mesangial cells and podocytes with infiltration of inflammatory cells and hemorrhage were observed. Also the necrosis of spermatogonia, spermatocytes, and spermatids were showed in testis tissues.
Shurooq Wesam Al-Shaibani et al (2022) [58]	male Wister Rats orally managed for 10 days	CaO-NPs (50and100) mg/kg from the body weight X-ray diffractometer, spectrophotometer	Two groups (50and100) mg/kg were observed a significantly increased in the weight of (testis tissue) also the level of testosterone hormone, as well as histology variations in the testis of treatment rats.
Ahsan Ullah et al (2023) [26]	Albino Rats (Rattus norvegicus intravenously (IV) to each rat with a 1-day interval, over a period of (24) days	Ca-NPs 25 and 50 mg/kg body weight Ca-NPs were purchased from- Sigma Aldrich USA and Merck (Germany)	No physical changes in conditions of (mortality, morbidity, behavioral, and neurological) signs were observed in rats of all groups. Different pathophysiological modifications such as significantly increased contents of oxidative parameters while reduced contents of antioxidant enzymes for example (reduced glutathione, peroxidase, catalase, and superoxide) in erythrocytes (RBC) of albino rats of group (B and C) were recorded. Results on various histo-architecture changes in (the testes, brain, as well as teeth) demonstrated various microscopic alterations in albino rats treated with high dosages of Ca-NPs.

4. Discussion

The human body contains several defense mechanisms against foreign objects, however, some or all of these mechanisms might not be able to stop NPs. To learn the truth about the health risks and harmful consequences of different kinds of NPs as well as how they are transported and develop inside the bodies of living things, several research has been carried out on a variety of animals in addition to humans. It has been discovered that numerous other factors affect the toxicity of NPs in addition to their size. These factors include the number of NPs, their chemical composition, their tendency to aggregate, the reactive nature of their surfaces, and their ability to dissolve. Determining the toxic effects and level of hazard on different human organs is made more challenging by these characteristics. Every kind of NP is predicted to have some level of toxicity, and it's possible that there is some inherent risk of toxicity in every process of NP preparation.

NPs can easily enter a human's body through the pores in their skin or through inhalation; among the most vulnerable areas for NP penetration are wounds and skin scars. Because of their small size, these NPs can pass through pulmonary barriers and enter the bloodstream. Because the NPs can disperse throughout the body's organs undetected, once they enter the veins and arteries, they will flow with the blood and be distributed throughout it. Numerous studies conducted recently on the effects of NPs on human health have demonstrated that these particles may accumulate in the lungs, brain, kidneys, heart, blood cells, central nervous system, liver, spleen, bones, and other organs, indicating that they may carry latent toxicity. Additionally, it has been discovered that some NP forms have a stimulating impact, which implies that they have the capacity to produce free radicals, which are typically responsible for the development of malignant tumors in the body. Since NPs have a large surface area compared to their size, they can cause severe reactions in body tissues and cause some tissues and liquids to condense on their surface, which can alter some enzyme and protein mechanisms of action. Additionally, inflammation is another way that NPs can weaken the body's defenses against germs.

The interaction of NPs with the human body can lead to toxicity, which has been the focus of the recently developed science of Nano toxicity research. When an element is reduced to the conventional nanoscale size, its chemical and physical characteristics shift, changing its potential toxicity even though the large-sized element may not be poisonous at first. The two most significant characteristics that are closely linked to poisoning are the small size and large surface area of the NPs. The skin, heart, kidneys, lungs, different kinds of cells, and other organs can all become poisoned by NPs. The handling of NPs and their applications in the manufacturing of goods must be controlled until their impacts on people and the environment are better understood, according to nonscientists. However, items made using nanotechnology or containing nanomaterials have proliferated in the market, ranging from food items to toothpaste, cosmetics, skin creams, and anti-wrinkle and UV lotions. All of this may cause the nanoparticles in these items to enter the body and get localized in different organs, which over time may cause poisoning or dysfunction

Lack of consumer awareness and the technology's seepage into the food and agriculture sectors pose further health risks. Food and agricultural items should not be included in this technological advancement, according to some scientists. According to the World Health Organization, nanotechnology has already permeated the food industry. However, before approving their adoption, materials and NPs used in the food industry and their packaging technology must be evaluated for their prospective effects on human health furthermore the environment. "The necessity of understanding the benefits and risks of nanotechnology" is another point of emphasis for the organization. Due to the excessive chemical activity of NPs, the majority of food additive approval systems in the past did not account for the particle size of the additive. As a result, all stakeholders—industry, regulators, and consumers—need to be aware of the situation surrounding them or have an open and honest discussion about it. This alters because the body processes these NPs differently from how it processes their previously approved bigger counterparts. Transit changes in the functions of liver and kidney were induced by a single or repeated in injection of (10)nm or (50)nm GNPs [51].

The levels of total aspartate aminotransferase, alanine aminotransferase, furthermore alkaline phosphatase changed, indicating that the CaO-NPs caused liver damage and may have caused hepatic toxicity within the experimental rats. These changes in specific parameters also showed that the liver was significantly affected in both experimental groups [56]. Without influencing fertility, repeated injection of GNPs was found to accumulate within the testes of male mice, lower levels of plasma testosterone, and raise the incidence of malformed epididymis sperm [53]. GNPs may raise hormone levels in males furthermore females, which would increase sterility [49]. NPs can penetrate cells through several routes and can have cytotoxic consequences [59].

5. Conclusion

Through the current study, we expect that nanotechnology will lead to many developments and updates in various health and healthcare fields, which often include drug delivery methods, new cancer treatments, and early detection methods for diseases, but it may also have undesirable effects. The increased rate of absorption is the main concern associated with manufactured nanoparticles. The surface area to volume ratio of materials increases when they are transformed into nanomaterials. The larger surface area (surface area per unit weight) leads to an increased rate of absorption, especially the reproductive system, liver, or even the kidneys in the presented research paper. However, the particles must be absorbed in sufficient quantities to cause health risks.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest exists among the Authors.

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