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Renal Toxic Effects of MgO NPs in Male Rats

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Abstract

Engineered nanomaterials are so tiny that they cannot be seen without special equipment; they are found in many industrial products today, consumer products, medicines, and food products. The small size and other properties of nanomaterials can make them very hazardous to human health. Magnesium oxide nanoparticles (MgO NPs), or metal oxides, have several advantages compared to other metal oxide nanoparticles because of their properties. Therefore, multiple uses of MgO NPs put human health at risk from prolonged exposure. The study aimed to determine how treatment with oral doses of MgO nanoparticles affects the kidneys of male rats through the oral route at 250 and 1000 mg/kg for 14 days, 28 days, and 56 days, respectively. Sixty mature male rats (2.5–3 months) were divided randomly into twelve groups of six rats each and gavaged with MgO NPs. The results observed a significant increase ($p<0.01$) in urea, creatinine, and uric acid; the histopathological examinations demonstrated necrotic debris inside the lumen of renal tubules; debris of lining epithelial cells inside the lumen of renal tubules; and the marked renal tubules were non-functional focal areas of necrosis and apoptosis. MgO NPs demonstrate potential issues with the kidneys and human health.

Keywords: Creatinine, MgO nanoparticles, necrosis, Urea, Uric acid.

التأثيرات السامة الكلوية لجزيئات أوكسيد المغنيسيوم النانوية في ذكور الجرذان

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الخلاصة

المواد النانوية المصممة هندسيًا صغيرة جدًا بحيث لا يمكن رؤيتها بدون معدات خاصة ، فهي توجد في العديد من المنتجات الصناعية اليوم والمنتجات الاستهلاكية والأدوية والمنتجات الغذائية. يمكن للخصائص الصغيرة الحجم وغيرها من المواد النانوية أن تجعلها شديدة الخطورة على صحة الإنسان. جزيئات أكسيد

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المغنيسيوم النانوية (MgO NPs) ، أكاسيد المعادن لها مزايا عديدة مقارنة بالجسيمات النانوية لأكسيد المعادن الأخرى بسبب خصائصها. لذلك ، فإن الاستعمالات المتعددة لـ MgO NPs تجعل صحة الإنسان في خطر التعرض لفترات طويلة. هدفت الدراسة إلى تحديد كيفية تأثير العلاج بجرعات فموية من جزيئات MgO النانوية على كلى ذكور الجرذان عن طريق الفم بجرعات (250 ، و 1000) مجم / كجم لمدة (14 ، 28 ، 56) يومًا. تم تقسيم 54 ذكرًا من الجرذان الناضجة (2.5 – 3 أشهر) بشكل عشوائي إلى 9 مجاميع من ستة جرذان لكل منها ، تم تطعيمها باستعمال MgO NPs. أظهرت النتائج زيادة معنوية عالية ($p < 0.01$) في اليوريا والكرياتينين وحمض اليوريك ، أظهرت الفحوصات النسيجية المرضية وجود حطام نخر داخل تجويف الأنابيب الكلوية ، وكانت الأنابيب الكلوية الملحوظة عبارة عن منطقة بؤرية غير وظيفية للنخر ، وموت الخلايا المبرمج تظهر جزيئات اوكسيد المغنسيوم النانوية مشاكل محتملة مع الكلى وصحة الإنسان.

1. Introduction

The concept of nanotechnology refers to manipulating matter on a molecular and atomic level to achieve properties (electrical, mechanical, magnetic, etc.) that are not otherwise possible. With nanotechnology, there are a variety of applications, ranging from medicine to computers. Nanotechnology is a field working on a scale of one nanometer to a billionth of a meter [1]. Nanotechnology is the future of medicine, as in drug delivery, injectable cancer medicines would be delivered in smaller volumes and the amount of the drug would be increased, allowing medication errors to be reduced [2]. Additionally, researchers are seeking ways to destroy cancerous cells within tumors, like using nanoshells. When injected inside a tumor, the intense heat generated by the nanoparticles after absorbing light of different frequencies will kill tumor cells without harming healthy ones [3]. Nanobots within the blood stream would be the ideal innovation in medicine, as they could patrol for abnormalities that might harm the body [4]. Nanotechnology is also used for water treatment. Food scientists use nanotechnology as nanosensors to identify any diseases that will be harmful to consumers, in addition to using nanotechnology to keep food fresher for longer periods of time [5] and [6].

A kidney is a bean-shaped organ on either side of the spinal column that regulates blood pressure and maintains the proper balance of water and minerals in the body. In addition, blood is continuously filtered through the kidneys, and waste products are excreted in urine. The blood enters each kidney through the renal artery, which then filters the blood through the nephrons to create urine. [7]. Nephrons make up each kidney; they contain porous blood vessels called the glomeruli. Fluid that will become urine leaks from these glomeruli into Bowman capsules. In the cortex, the outer layer of the kidney, the glomeruli are located; they drain urine into the tubules of the medulla and into the collecting ducts. Urine drains into the bladder via the ureters, which connect each kidney to it. and then through the urethra, the tube that leads outside the body [8].

2. Materials and Methods

2.1. Magnesium Oxide Nano powder General Description and Preparation

Magnesium oxide nanopowder is a fine white powder composed of > 99% MgO and ranging about 20 nm in diameter. It was purchased from US Research Nanomaterials, Inc. This nanopowder had the following characteristics:

• Nano powder (MgO) purity > 99%, APS: 20 nm, APS color: white, morphology: polyhedral, Bulk Density: 0.145 g/cm3, True Density: 3.58 g/m3.

Magnesium oxide was prepared in two different doses:

1) Low-dose rat groups: 250 mg/kg of MgO NPs.
2) High-dose rat groups: 1000 mg/kg of MgO NPs.

stirred with deionized water, blended continuously for several minutes using a vortex, and each rat orally gavaged with a dose of 1 cc of the suspension, dosing based on its own weight.

2.2. Animal Care, and Experimental Research Design

Sixty male rats (Rattus norvegicus) were used as models for mammals. Approximately 2.5- to 3-month-old males were purchased, grouped, and housed at home. Under climate-controlled conditions, they were kept in plastic cages with a metal network cover at a temperature of 25 °C and a light-dark cycle of 10:14. The cages were usually cleaned out every day to carry their scent, making the rats more relaxed with clean and fresh drinking water, bedding, and food. Water was provided from a bottle, and pelleted food was provided from special water bottles.

For analyzing physiological and histological parameters, in twelve groups of six rats each, 60 male rats were randomly divided after an adaptation period of about a week. Sorted as follows: Group 1, 2, and 3: (control) did not receive any dose of MgO NPs for 14, 28, and 56 days subsequently, while groups (4, 6, and 8) in these experimental groups were administered with 250 mg/kg MgO nanoparticles every 24 hours for 14, 28, and 56 days, respectively, while groups (5, 7, and 9), respectively, received 1000 mg/kg MgO nanoparticles every 24 hours for 14, 28, and 56 days subsequently.

2.3. Samples Collection and Direct Examination

As part of the experiment, the rats were fully anesthetized (to prevent them from becoming stressed) using diethyl ether for several minutes, and blood samples were collected through heart punctures. A total of 8 ml of blood was obtained from each rat, of which 6 ml were used as sera (for the physiological study). After 5 minutes of centrifugation at 3000 rpm and storage at -20 °C for biochemical analysis, the animals were cut open and their right and left kidneys removed. The kidneys were then rinsed in normal physiological saline (0.9% NaCl), blotted with filter paper, and fixed in neutral buffered formalin (10%) for histopathology.

2.4. Biochemical Tests for Kidney Functions

Biochemical tests were performed depending on the sandwich enzyme-linked immunosorbent (ELISA) technique:

1. Measurement of blood urea using the enzymatic colorimetric method.
2. The measurement of serum creatinine was determined by the photometric method.
3. Measurement of uric acid using the enzymatic colorimetric technique.

2.5. Histological Preparation: In order to prepare histological sections, the method of grossing [9] is a process for examining pathology specimens, trimming them to the appropriate size, and selecting the best part for further microscopic examinations for diagnostic purposes.

2.6. Statistical Analysis: The Statistical Analysis System (SAS) (2012) program was used as a procedure that performs analysis of variance (ANOVA), and finding the least significant difference (LSD) test was used to determine if there was any significant effect from different factors by comparing the study mean values.

3. Results and Discussion:

The results of the biochemical assay for rat urea levels are presented in Table 1. Rats administered (250 and 1000) mg/kg of MgO NPs exhibited a significant increase ($p<0.01$) in urea serum levels during (2, 4, and 8) weeks of administration (51.375 ±0.02, and 53.643 ±0.06), (55.455 ±0.07, and 58.271 ±0.09), and (70.670±0.06, and 78.540±0.06) mg/dl, respectively, as compared to their normal controls (38.016±0.08), (38.113±0.06), and (38.025±0.20) mg/dl, respectively). Moreover, statistical data of urea serum levels showed a significant increase ($p<0.01$) in low dose administration (51.375 ±0.02), (55.455 ±0.07), and

(70.670 ±0.06) mg/dl when comparing between the treated groups themselves during (2, 4, and 8) weeks, respectively, and in high dose administration (53.643 ±0.06) and (58.271 ±0.09) for 2 and 4 weeks, respectively, with the highest level in 8-week duration (78.540 ±0.06) mg/dl, when comparing between the treated groups themselves.

Table 1: MgO NPs' Effect on Rat Urea Level in Male Rats

Groups	Mean ± SE of Urea			LSD value
	2 Weeks	4 Weeks	8 Weeks	
Control	38.016 ±0.08 A a	38.113 ±0.06 A a	38.025 ±0.20 A a	0.391 NS
MgO NPs: 250 mg/kg	51.375 ±0.02 A b	55.455 ±0.07 B b	70.670 ±0.06 C b	0.172 **
MgO NPs: 1000 mg/kg	53.643 ±0.06 A c	58.271 ±0.09 B c	78.540 ±0.06 C c	0.212 **
LSD value	0.177 **	0.223 **	0.382 **	---

**(A, B, C) represents the difference among groups (within a row) when time is a variable factor and concentration is a fixed factor.

**(a, b, c) represents the difference among groups (within a column) when concentration is a variable factor and time is a fixed factor.

** = high significant effect with a p value of ($p< 0.01$).

NS = nonsignificant effect

Similarly, the renal level of serum creatinine, in Table 2, was significantly higher ($p<0.01$) in (2, 4, and 8) weeks (0.825 ±0.006), (1.333 ±0.009), and (1.719 ±0.003) mg/dl, respectively, with the low dose (250 mg/kg) of MgO NPs administration. When comparing between the treated groups themselves, the serum creatinine level was also significantly higher ($p<0.01$) in the high dose (1000 mg/kg) of MgO NPs administration during (2, 4, and 8) weeks between the treated groups themselves (0.876 ±0.009), (1.421 ±0.005), and (1.862 ±0.004) mg/dl, respectively.

Table 2: Effects of MgO NPs on serum creatinine levels in male rats

Groups	Mean ± SE of Creatinine			LSD value
	2 Weeks	4 Weeks	8 Weeks	
Control	0.543±0.004 A a	0.547±0.005 A a	0.547±0.002 A a	0.012 NS
MgO NPs: 250 mg/kg	0.825 ±0.006 A b	1.333 ±0.009 B b	1.719 ±0.003 C b	0.021 **
MgO NPs: 1000 mg/kg	0.876 ±0.009 A c	1.421 ±0.005 B c	1.862 ±0.004 C c	0.019 **
LSD value	0.021 **	0.020 **	0.009 **	---

**(A, B, C) represents the difference among groups (within a row) when time is a variable factor and concentration is a fixed factor.

**(a, b, c) represents the difference among groups (within a column) when concentration is a variable factor and time is a fixed factor.

** = High significant effect with a p value of ($p< 0.01$).

NS = nonsignificant effect

Low and high doses of MgO NPs showed a significant increase ($p<0.01$) in (2, 4, and 8) weeks (0.825 ±0.006, and 0.876 ±0.009), (1.333 ±0.009, and 1.421 ±0.005), and (1.719

±0.003, and 1.719 ±0.003) mg/dl, respectively, compared to their controls (0.543±0.004), (0.547±0.005), and (0.547±0.002) mg/dl, respectively.

There were significantly high ($p<0.01$) uric acid serum levels revealed in Table 3 in (2, 4, and 8) weeks of MgO NPs orally administered to rats in low and high doses (51.375 ±0.02, and 53.643 ±0.06), (55.455 ±0.07, and 58.271 ±0.09), and (70.670 ±0.06, and 78.540 ±0.06) mg/dl, respectively, as compared to their control groups (38.016 ±0.08), (38.113 ±0.06), and (38.025 ±0.20). The administration-related effect of MgO NPs to the rats on uric acid serum levels in low and high doses was observed as a significant increase ($p<0.01$) in (2, 4, and 8) weeks (51.375 ±0.02), (55.455 ±0.07), and (70.670 ±0.06) mg/dl for the low doses, respectively, and (53.643 ±0.06), (58.271 ±0.09), and (78.540 ±0.06) mg/dl, respectively).

Table 3: Effects of MgO NPs on serum uric acid levels in male rats

Groups	Mean ± SE of Uric Acid			LSD value
	2 Weeks	4 Weeks	8 Weeks	
Control	4.835 ±0.005 A a	4.855 ±0.003 A a	4.960 ±0.20 A a	0.365 NS
MgO NPs: 250 mg/kg	4.685 ±0.05 A a	4.093 ±0.03 B b	3.297 ±0.04 C b	0.129 **
MgO NPs: 1000 mg/kg	4.019 ±0.13 A b	3.975 ±0.02 B c	2.814 ±0.04 C c	0.247 **
LSD value	0.266 **	0.084 **	0.365 **	---

**(A, B, C) represents the difference among groups (within a row) when time is a variable factor and concentration is a fixed factor.

**(a, b, c) represents the difference among groups (within a column) when concentration is a variable factor and time is a fixed factor.

** = High significant effect with a p value of ($p< 0.01$).

NS = nonsignificant effect

kidneys of control group rats (Figure 1) showed a normal appearance and consisted of glomerular renal tubules (proximal and distal convoluted tubules). Morphological changes in renal rats started to appear after two weeks. At low doses (250 mg/kg) (Figure 2-A), proximal and distal epithelial cells degenerated, and there were a few apoptotic cells. At high doses (1000 mg/kg) (Figure 2-B), blood vessels became clogged, and there were degenerative changes in renal epithelial cells, apoptosis, and a decrease in the number of epithelium-lining cells. Also, after 4 weeks (low dose) (Figure 3-A), treated rat kidneys showed congestion of blood vessels, degeneration of epithelial cells, and apoptosis. At high doses (Figure 3-B), degeneration in epithelial cells and apoptosis were seen, along with necrotic debris inside the lumen of renal tubules and a focal area of necrotic renal tubules. Also, after 8 weeks (Figure 4-A), rats who were given 250 mg/kg NPs had a clogged lumen of renal tubules, necrotic debris with apoptosis, and epithelial cells that were degenerating. After eight weeks (Figure 4-B), sections of the kidney showed degenerating and apoptotic epithelial cells and pieces of lining epithelial cells in the lumen of the renal tubules. The marked renal tubules were non-functional.

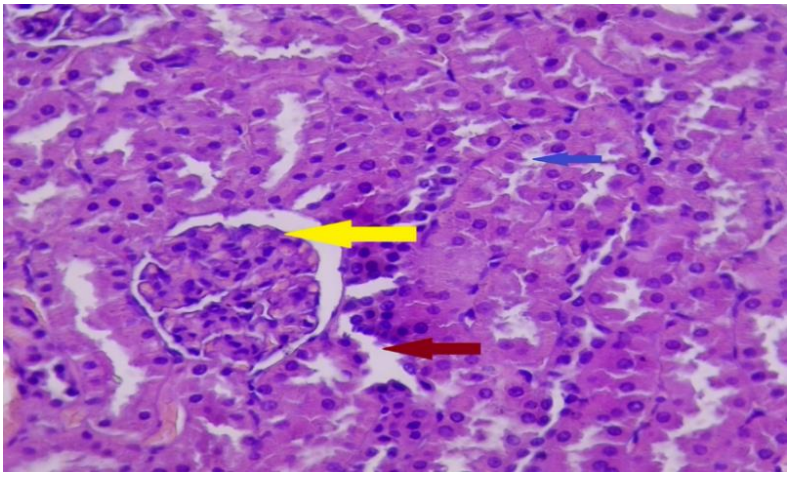

Figure 1: A cross section of the kidney (control group) shows a normal histological appearance, which is composed of glomerular renal tubules (proximal and distal convoluted tubules). (40 X) (H&E)

Normal Glomeruli Normal distal tubules Normal proximal tubules

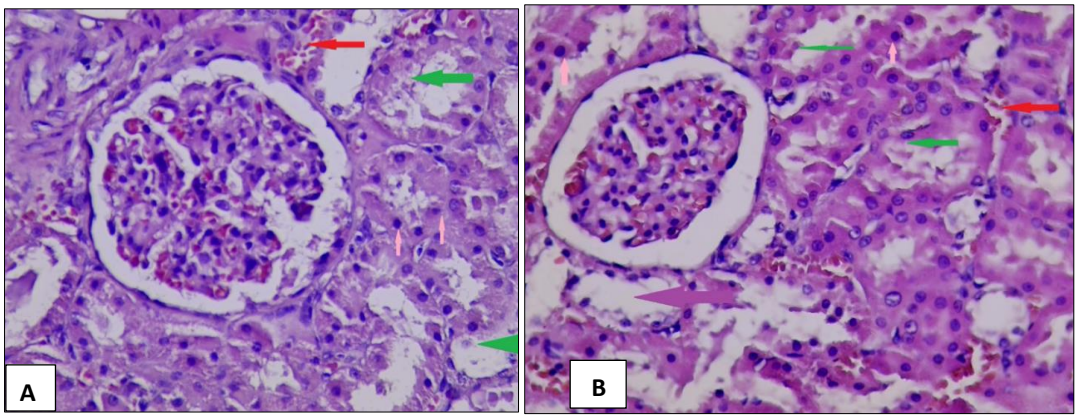

Figure 2: A: cross section of a rat kidney After 2 weeks (low dose), the group shows degenerative changes in proximal and distal epithelial cells with rare apoptotic cells. (40 X) (H&E)

B: After 2 weeks in the high dose group, the rat kidney cross section shows congestion of blood vessels, degenerative changes of renal epithelial cells, and apoptosis with a decrease in the number of the lining epithelial cells. (40 X) (H&E)

Congestion Apoptosis

Degeneration Decrease in the number of the lining epithelial cells

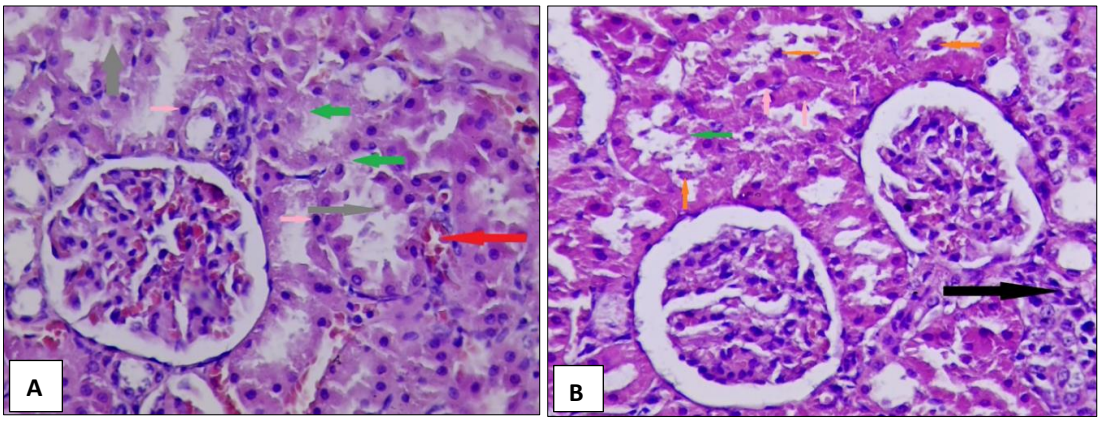

Figure 3: A: Kidney cross-section shows a 4-week (low dose) group with congestion of blood vessels, degeneration of epithelial cells, and apoptosis. (40 X) (H&E)

B: This cross-section of the kidney shows the effects of the high-dose group after 4 weeks: Degeneration of epithelial cells and apoptosis; necrotic debris inside the lumen of renal tubules; focal area of necrotic renal tubules(40 X)(H&E)

Congestion
Degeneration
Apoptosis
Necrotic debris
Necrosis

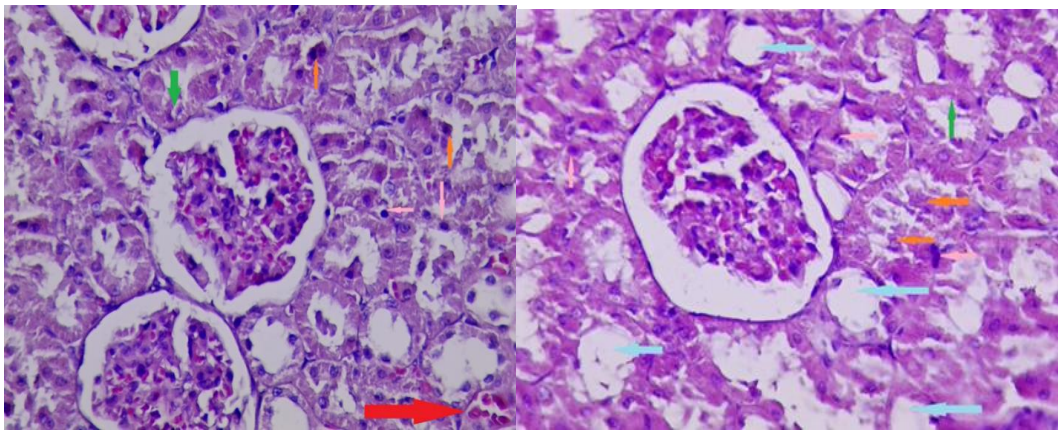

Figure 4: A: This cross-sectional view of the kidney shows that after 8 weeks (low dose), there is congestion, necrotic debris inside the lumen of renal tubules, apoptosis, and degeneration of epithelial cells. (40 X) (H&E)

B: A cross-section of the kidney shows that the 8-week (high dose) group had degenerative and apoptotic epithelial cells, debris of lining epithelial cells inside the lumen of renal tubules, and marked renal tubules that were non-functional. (40 X) (H&E)

Congestion
Degeneration
Necrotic debris
Apoptosis
Non-functional renal tubules

Removal and excretion of plasma constituents, including nanoparticles, into the urine is a major function of the kidneys to eliminate excess waste products and ions from the blood. For this reason, they are considered one of the most important secondary target organs. The use of nanoparticles that can induce renal toxicity should be carefully evaluated [10]. In order to evaluate the toxicity and bioaccumulation of MgO NPs in vital organs, male rat groups were administered vitamin E with MgO NPs (62.5, 125, 250, and 500) mg/kg body weight orally for 28 days, while other groups were exposed to a combination of vitamins C and E with magnesium NPs. Results exhibited adverse effects in blood parameters, with a significant increase in serum ROS and histological damage to the kidney [11]. In a previous study, it was

reported that numerous types of nanoparticles are capable of passing biological barriers and affecting vital organs, including the kidneys and liver [12]. Upon inhalation exposure to different welding methods using different steel base materials, it was found that magnesium concentrations in the kidney, liver, and lungs of mice were extremely increased at both sampling times (24 and 96 hours) [13]. Once the nanoparticles get into the blood circulation, they are capable of distributing and accumulating in different organs such as the lungs, kidneys, and liver, causing oxidative stress in these organs and inhibiting the effects of antioxidants [14]. The biochemical indices for the kidney sections of male and female rats exposed to three different dosages of MgO NPs (250, 500, and 1000 mg/kg) orally for 28 days showed significant increases in kidney homogenates with histopathological damage found in the kidney tissues of rats treated with 1000 mg/kg of MgO nanoparticles; moreover, there was swelling of renal capsules and disassembling of the glomerulus observed in kidney sections [15].

In contrast, findings showed that (250 and 500 µg/mL) magnesium oxide NPs increased levels of creatinine and urea in comparison with the control group, but no histological renal changes were found [16]. Treatment with MgO NPs improved kidney function and reduced inflammation, in addition to raising the level of hemoglobin and thereby reducing anemia. When magnesium oxide was administered subcutaneously for 28 days at 10000 µg/mL, serum urea and serum creatinine decreased significantly ($p = 0.01$) during the study [17]. In a rat model, both in vitro and in vivo data demonstrated a non-significant change in urea, creatinine, and uric acid serum levels as compared with the control group [18]. [19] postulated that cisplatin nanocomposite, which was formulated from chitosan coated with cisplatin and MgO NPs, may be a valuable possible drug that reserves renal function and structure by reducing the cytotoxicity of cisplatin. Together, the experimental measurements and theoretical simulations demonstrated that MgO NPs have massive features for improving the treatment specificity of in vivo hind legs of rabbits and in vitro pig tissues injected with magnesium nanoparticles after exposure to laser irradiation. The use of magnesium nanoparticles in hyperthermia therapy demonstrates promising results, and it is safe to be used in clinics in the near future [20]. Following keratopathy with or without diabetes mellitus, a combination of magnesium hydroxide nanoparticles repairs and enhances wounded epithelial corneas in rabbits. The magnesium hydroxide combination was considered a potent drug to cure severe keratopathy [21]. Dietary probiotics exhibit beneficial effects on intestinal and intrinsic health for a long time; never the less, the gastrointestinal tract may lose its vitality throughout the absorption process, resulting in meager intestinal delivery of the probiotic's active ingredients. The ability of nanotechnology to increase bioavailability has been used to combat this problem. [22]. A minimal histological alteration was observed in both MgO doses (100 and 200 mg/kg) with non-effective alterations in serum creatinine in treated rats, both male and female, depending on the safety of zein-coated magnesium oxide nanowires, which can be used for the preparation of new dental formulations [23]. Based on testing magnesium oxide nanoparticles, as they had not previously been discovered to have a toxicity or safety level (MgO NPs) <100 nm in isolated pancreatic islet cells, the results indicated a significant reduction in oxidative stress markers like ROS and lipid peroxidation (LPO), which were treated with magnesium nanoparticles for 24 h at a 100 µg/ml concentration, significantly increased the level of insulin secretion, and decreased caspase-9 inhibitory activity [24].

Nanoparticles are complex, they might be risky, and the damage that is occurring to the kidneys as a result of using nanoparticles can occur in three different ways: through pro-inflammatory cytokines, induction of apoptosis, and formation of free radicals that cause damage to the membrane and macromolecules [25]. The high doses of NPs and the duration of the study could explain why NPS increases urea, total protein, and creatinine levels. As a

consequence of this degeneration and necrosis of kidney cells, as well as damage to peritubules, secretion was impaired, which resulted in elevated blood levels of urea. Because of the imbalance in kidney functions, creatinine and total protein levels in serum also increased [26].

To mark the morphological changes caused by nanoparticle exposure, a histopathological examination is necessary to assess the toxicological effects on the kidney. The cytotoxic analysis was performed after acute oral exposure to MgO nanoparticles in female rats. Results revealed that in kidney tissues, there is a significant accumulation of magnesium with swelling in the renal glomerulus and a highly significant increase in the creatinine levels at all three doses (100, 500, and 1000 mg/kg) [27].

As a general rule, it appears that engineered nanoparticles have greater toxicity when they are smaller than their larger counterparts; they appear to be toxic through multiple mechanisms, including membrane damage, oxidative stress, cytoskeletal changes, mitochondrial damage, necrosis, and apoptosis [28]. There is some evidence that NP-induced oxidative stress occurs as a result of mitochondrial dysfunction, activation of stress-related cell signaling pathways, and DNA damage, leading to cell cycle arrest and apoptosis. It is also possible that catalase function and protein oxidation may be modified in response to NP-induced oxidative stress [29] and [30]. Nanoparticles that are charged tend to accumulate more in target organs than NPs that are uncharged; the ionic forms of ZnO NPs were shown to accumulate more in organs such as the kidneys, liver, and lungs following oral administration [31]. Three different doses of 25, 50, and 100 mg/kg zinc oxide nanoparticles (ZnO NPs) were administered intraperitoneally to albino male mice for 2 and 4 weeks to evaluate the acute and sub-chronic toxicity effects. The histopathological sections showed swelling and dilation of kidney tubules, thickening of intestinal villi, and moderate interstitial pneumonia, especially with a high dose [32]. For the assessment of the effects of titanium dioxide nanoparticle suspensions (TiO2) given in two doses (150, 600 mg/kg) intraperitoneally, male albino mice were used, creatinine was increased in all groups, whereas uric acid increased in many cases, with the highest mean value recorded after 14 days of exposure to 150mg/kg and 30 days of exposure to 600mg/kg, in the fourteen-day and thirty-day treatment groups, urea levels decreased, remarkably TiO2 NPs accumulated mainly in the spleen, followed by the liver and kidneys, the histological alterations included glomerular congestion, tubular congestion, atrophy, chronic inflammatory cells infiltration, and dilated tubules with flat, atrophied lining epithelium in the kidneys, which makes it difficult to eliminate leftovers caused by nanoparticles' metabolic and structural disruptions [33].

The majority of studies have shown that heavy metals are somehow toxic to humans [34]. Kidneys are responsible for maintaining health by excreting the toxins needed to be released with urine, but toxic materials that are difficult to excrete will accumulate in the kidneys at elevated levels, resulting in kidney damage. This indicates that the toxicity is inflicted via different alterations through numerous mechanisms such as oxidative stress, inhibition of cell division, inflammatory changes in kidney tubules, and eventually cell death, leading to renal injury and dysfunction. Due to the toxicity of NPs, oxidative stress is one of the most important mechanisms. It is triggered by either a depletion of antioxidants or an increase in the production of reactive oxygen species and reactive nitrogen species. The polymer-based NPs need to be assessed for their bioavailability, degradation, and toxicity. The circulating NPs after administration tend to accumulate in vital organs such as the brain, spleen, kidney, and liver, causing variable toxicities.

4.Conclusion

According to the results, MgO NPs demonstrate potential harm to kidney function, histology, and human health. Based on the results of several studies, it seems that MgO NPs clump together in different animal kidney models, interact with the endothelium of the renal tubules, and may cause oxidative stress. Human-consumed products should be cautious about excessive use of MgO NPs. The polymer-based NPs need to be assessed for their bioavailability, degradation, and toxicity.

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6. Ethical Approval

Authors have signed on to ethical consideration's approval (Ref. No.: BCSMU/0122/0004Z) for standards of research involving animals.

7. Conflict of Interest: The authors declare that they have no conflicts of interest.

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