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Moringa oleifera Seed Extract Alleviates Silver Nanoparticle Hepatorenal Toxicity by Attenuating Oxidative Stress in Mice

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مستخلص بذور المورينجا أوليفيرا يخفف السمية الكبدية والكلوية للجسيمات النانوية الفضية عبر التخفيف من الإجهاد التأكسدي في الفئران

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Abstract:

Background: The widespread application of silver nanoparticles (AgNPs) in consumer products raises concerns about their potential organ toxicity, primarily mediated through oxidative stress. *Moringa oleifera* (MO) is a plant renowned for its potent antioxidant properties. This study investigated the protective role of *Moringa oleifera* seed extract (MSE) against AgNP-induced hepatorenal damage in mice. **Methods:** Twenty-eight male albino mice were randomly divided into four groups (n=7): Control group received saline; MSE group received MSE (500 mg/kg/day, orally); AgNPs group received AgNPs (50 mg/kg/day, intraperitoneally); and AgNPs + MSE group received both MSE and AgNPs concurrently for 14 days. Biochemical markers of liver function (ALT, AST, ALP) and kidney function (creatinine, urea), as well as oxidative stress markers (MDA, GSH, SOD) in liver and kidney tissues, were assessed. Histopathological examinations of both organs were also performed. **Results:** AgNP administration induced significant hepatorenal toxicity, evidenced by elevated serum ALT, AST, ALP, creatinine, and urea levels, a marked increase in tissue MDA, and a decrease in GSH and SOD activities. Histopathological analysis revealed severe hepatic necrosis, inflammatory cell infiltration, and renal tubular degeneration. Co-treatment with MSE significantly ameliorated these changes, normalizing the biochemical parameters, restoring antioxidant enzyme activities, and markedly improving the tissue architecture. **Conclusion:** The findings demonstrate that *Moringa oleifera* seed extract effectively mitigates AgNP-induced hepatorenal toxicity, primarily through its potent antioxidant activity. MSE represents a promising natural agent for protection against nanomaterial-induced organ damage.

Keywords: *Moringa oleifera*, silver nanoparticles, oxidative stress, hepatotoxicity, nephrotoxicity, antioxidant.

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الملخص

الخلفية :يؤدي الاستخدام واسع النطاق للجسيمات النانوية الفضية (AgNPs) في المنتجات الاستهلاكية إلى إثارة مخاوف بشأن سميتها العضوية المحتملة، والتي يُمثل الإجهاد التأكسدي الآلية الرئيسية لها. وتشتهر نبات المورينجا أوليفيرا (MO) بخصائصه المضادة للأكسدة. هدفت هذه الدراسة إلى تقييم الدور الوقائي لمستخلص بذور المورينجا أوليفيرا (MSE) ضد الضرر الكبدي والكلوي المُحفَّز بالجسيمات النانوية الفضية في الفئران. **الطرق :**تم تقسيم ثمانية وعشرين فأراً من ذكور الفئران البيضاء عشوائياً إلى أربع مجموعات (7 حيوانات في كل مجموعة): المجموعة الضابطة (تلقت محلولاً ملحياً)، مجموعة MSE (تلقت المستخلص بجرعة 500 ملغ/كغ/يوم عن طريق الفم)، مجموعة AgNPs (تلقت الجسيمات النانوية بجرعة 50 ملغ/كغ/يوم داخل الصفاق)، ومجموعة المعالجة المشتركة AgNPs + MSE (تلقت كلا المادتين معاً) ولمدة 14 يوماً. تم قياس المؤشرات الكيميائية الحيوية لوظائف الكبد) إنزيمات ALT, AST, ALP)ووظائف الكلى (الكرياتينين واليوريا)، وكذلك مؤشرات الإجهاد التأكسدي) مالونديالدهيدMDA ، الجلوتاثيونGSH ، سوبرأكسيد ديسموتاز (SOD في أنسجة الكبد والكلى. كما أُجريت فحوصات نسيجية مرضية لكلا العضوين. **النتائج :**أدى تعاطي الجسيمات النانوية الفضية إلى سمية كبدية وكلوية واضحة، تجلت في ارتفاع مستويات إنزيمات الكبد والكرياتينين واليوريا في مصل الدم، وزيادة معنوية في مستوى MDAفي الأنسجة، وانخفاض في نشاط كل من GSH و .SODوأظهر التحليل النسيجي المرضي وجود نخر حاد في الكبد، وتسلل للخلايا الالتهابية، وتنكس في الأنابيب الكلوية. وقد خففت المعالجة المشتركة مع مستخلص البذور هذه التغيرات بشكل ملحوظ، حيث أدت إلى عودة المؤشرات الكيميائية الحيوية إلى مستوياتها الطبيعية، واستعادة نشاط الإنزيمات المضادة للأكسدة، وتحسين مُلموس في البنية النسيجية للكبد والكلى. **الاستنتاج :**توضح نتائج هذه الدراسة أن مستخلص بذور المورينجا أوليفيرا يخفف بشكل فعال السمية الكبدية والكلوية المُحفزة بالجسيمات النانوية الفضية، وذلك يعزى بشكل رئيسي إلى نشاطه المضاد للأكسدة. وبالتالي، يمثل هذا المستخلص عاملاً طبيعياً واعداً للحماية من الضرر العضوي الناجم عن المواد النانوية.

الكلمات المفتاحية :المورينجا أوليفيرا، الجسيمات النانوية الفضية، الإجهاد التأكسدي، سمية كبدية، سمية كلوية، مضادات الأكسدة.

1. Introduction

Silver nanoparticles (AgNPs) are among the most commercially exploited nanomaterials due to their unique antimicrobial, electrical, and catalytic properties, leading to their incorporation into a vast array of products, including textiles, medical devices, and cosmetics (Vance et al., 2015). However, this increased exposure has raised significant concerns regarding their potential toxicity to humans and the environment. Upon entering the systemic circulation, AgNPs tend to accumulate primarily in the liver and kidneys, the major organs for detoxification and excretion, making them primary targets for AgNP-induced damage (Zhang et al., 2019).

A primary mechanism underlying AgNP toxicity is the induction of oxidative stress. AgNPs can generate reactive oxygen species (ROS), leading to lipid peroxidation, protein denaturation, and DNA damage, ultimately resulting in cellular apoptosis and necrosis (Akter et al., 2018). This oxidative assault manifests clinically as elevated serum markers of liver injury (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]) and kidney dysfunction (creatinine, urea), accompanied by characteristic histopathological alterations.

In recent years, there has been a growing interest in using natural antioxidants to counteract chemical-induced organ toxicity (Salem et al 2021, Salem, & Lakwani, 2024).*Moringa oleifera*, often called the "miracle tree," is a plant whose seeds are particularly rich in potent antioxidant compounds, including flavonoids, phenolic acids, and glucosinolates (Leone et al., 2016). Previous studies have demonstrated the hepatoprotective and renoprotective effects

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of *Moringa* extracts against various toxins (Al-Owaisi et al., 2014). However, its efficacy against AgNP-induced hepatorenal toxicity remains largely unexplored.
This study was designed to evaluate the hypothesis that *Moringa oleifera* seed extract (MSE) can alleviate AgNP-induced hepatorenal damage in mice and to elucidate the role of oxidative stress attenuation in this protective mechanism.

2. Materials and Methods

2.1. Chemicals and Extract Preparation

Silver nanoparticles (AgNPs, <50 nm, spherical, PVP-coated) were purchased from Nanocs Inc. (USA). *Moringa oleifera* seeds were authenticated, and a methanolic extract (MSE) was prepared using the Soxhlet apparatus. The extract was concentrated and stored at -20°C until use (Bilen et al 2020).

2.2. Experimental Animals

Twenty-eight healthy male albino mice (25-30 g) were housed under standard conditions (12h light/dark cycle, 25 ± 2°C) with free access to a standard pellet diet and water. All experimental procedures were approved by the Animal Ethics Committee and conducted in accordance with the university guidelines.

2.3. Experimental Design

After one week of acclimatization, the mice were randomly divided into four groups (n=7 per group):
Group I (Control): Received normal saline orally for 14 days.
Group II (MSE): Received MSE (500 mg/kg/day, orally) for 14 days (Al-Owaisi et al., 2014).
Group III (AgNPs): Received AgNPs (50 mg/kg/day, intraperitoneally) for 14 days (Zhang et al., 2019).
Group IV (AgNPs + MSE): Received both MSE (500 mg/kg/day, orally) and AgNPs (50 mg/kg/day, i.p.) concurrently for 14 days.

2.4. Sample Collection

Twenty-four hours after the last dose, blood was collected from the retro-orbital plexus under mild anesthesia. Serum was separated for biochemical analysis. The mice were then euthanized, and liver and kidney tissues were promptly excised. One portion was homogenized in cold phosphate buffer for oxidative stress assays, and another portion was fixed in 10% formalin for histopathology.

2.5. Biochemical Assays

Liver and Kidney Function: Serum levels of ALT, AST, ALP, creatinine, and urea were measured using standard commercial diagnostic kits.
Oxidative Stress Markers: Tissue homogenates were used to assess:

- **Malondialdehyde (MDA)** level as a marker of lipid peroxidation (Ohkawa et al., 1979).
- **Reduced Glutathione (GSH)** level (Ellman, 1959).
- **Superoxide Dismutase (SOD)** activity (Marklund & Marklund, 1974).

2.6. Histopathological Examination

Formalin-fixed tissues were processed, embedded in paraffin, sectioned at 5µm, and stained with Hematoxylin and Eosin (H&E). The slides were examined under a light microscope by a pathologist blinded to the treatment groups.

2.7. Statistical Analysis

Data are expressed as mean ± standard deviation (SD). Statistical significance was determined by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test using GraphPad Prism software (v.9). A p-value of < 0.05 was considered statistically significant.

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3. Results and Discussion

3.1. MSE Ameliorates AgNP-Induced Liver and Kidney Dysfunction

Administration of AgNPs resulted in a significant ($p < 0.01$) increase in serum ALT, AST, and ALP levels compared to the control group, indicating severe hepatocellular damage and biliary obstruction (Table 1). Similarly, a marked elevation ($p < 0.01$) in serum creatinine and urea levels was observed, signifying impaired renal function. Treatment with MSE alone showed no adverse effects. Importantly, co-administration of MSE with AgNPs (Group IV) significantly ($p < 0.05$) attenuated these elevations, bringing the biochemical parameters closer to normal levels.

Table 1: Effect of MSE on Serum Biochemical Parameters in AgNP-treated Mice.

Group	ALT (U/L)	AST (U/L)	ALP (U/L)	Creatinine (mg/dL)	Urea (mg/dL)
Control	35.2 ± 3.1	85.5 ± 6.8	145.3 ± 12.1	0.38 ± 0.04	32.1 ± 3.5
MSE	33.8 ± 2.9	82.1 ± 7.2	139.8 ± 10.5	0.36 ± 0.05	30.8 ± 2.9
AgNPs	128.6 ± 11.4*	245.7 ± 20.3*	320.5 ± 25.8*	0.95 ± 0.08*	78.4 ± 6.9*
AgNPs+MSE	62.4 ± 5.7**	132.6 ± 11.5**	188.2 ± 15.3**	0.52 ± 0.06**	45.2 ± 4.1**

Data are Mean ± SD (n=7). **p < 0.01 vs. Control; ** p < 0.01 vs. AgNPs group.*

3.2. MSE Attenuates AgNP-Induced Oxidative Stress

The AgNPs group exhibited a profound state of oxidative stress in both liver and kidney tissues; characterized by a significant ($p < 0.01$) increase in MDA levels and a concomitant decrease ($p < 0.01$) in GSH content and SOD activity compared to the control group (Figure 1). Co-treatment with MSE effectively ($p < 0.01$) reversed these trends, significantly lowering MDA levels and restoring the activities of the antioxidant defenses (GSH and SOD). This indicates that the primary mechanism of MSE's protection is the scavenging of ROS and the enhancement of the endogenous antioxidant system.

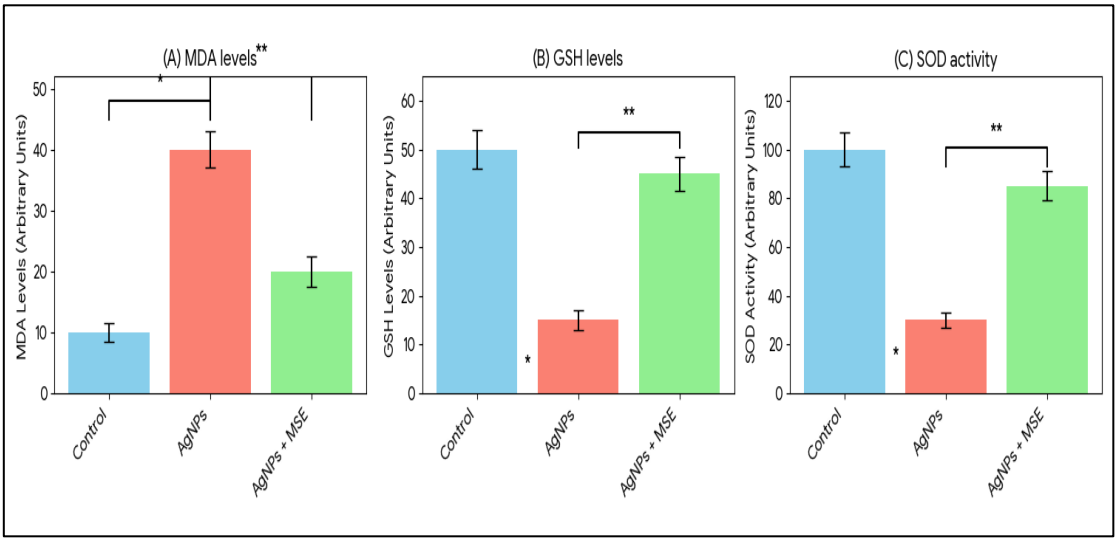

Figure 1: Oxidative Stress Markers in Liver Tissue.

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(A) MDA levels were significantly increased in the AgNPs group and reduced by MSE co-treatment. (B) GSH levels and (C) SOD activity were depleted by AgNPs and restored by MSE. **p < 0.01 vs. Control; ** p < 0.01 vs. AgNPs group.*

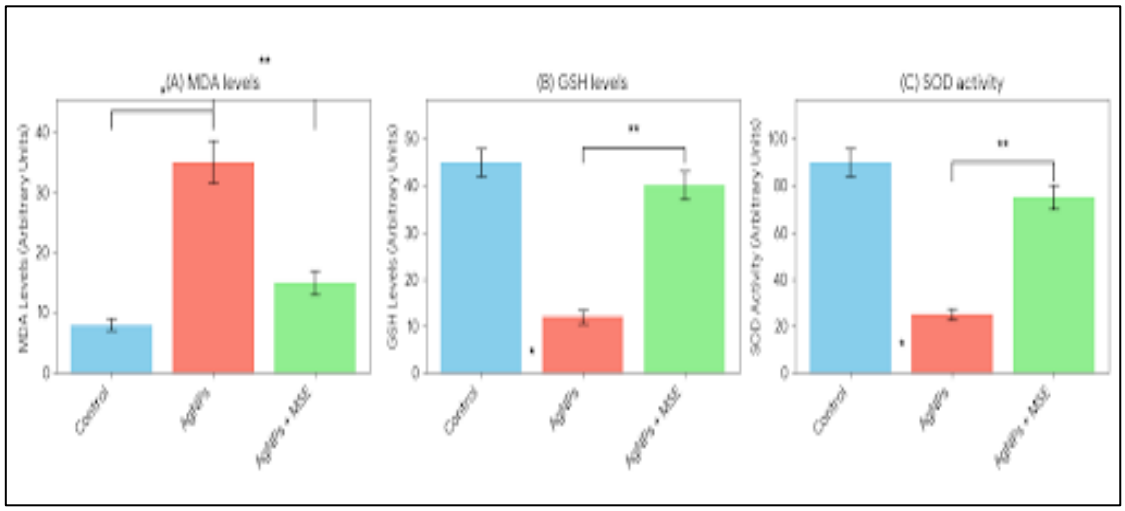

Figure 2: Oxidative Stress Markers in kidney Tissue.

(A) MDA levels were significantly increased in the AgNPs group and reduced by MSE co-treatment. (B) GSH levels and (C) SOD activity were depleted by AgNPs and restored by MSE. **p < 0.01 vs. Control; ** p < 0.01 vs. AgNPs group.*

3.3. Histopathological Findings Corroborate Biochemical Data

Histopathological examination provided clear visual evidence of AgNP toxicity and MSE protection.

Liver: The control and MSE-only groups showed normal hepatic architecture. The AgNPs group exhibited severe centrilobular necrosis (N), vacuolar degeneration (V), and infiltration of inflammatory cells (I). The AgNPs+MSE group showed near-normal liver structure with only mild, focal inflammation (Figure 3).

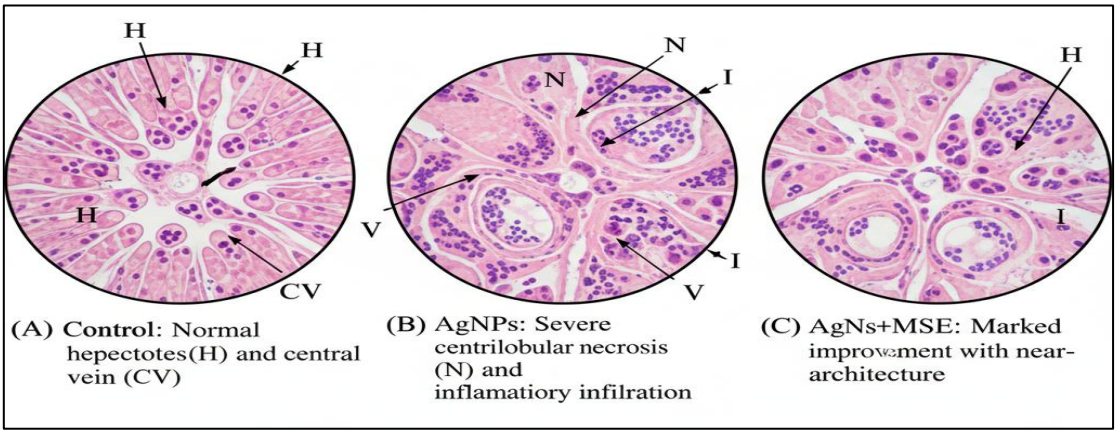

Figure 3: Photomicrographs of Liver Sections (H&E, 400x).

(A) Control: Normal hepatocytes (H) and central vein (CV). (B) AgNPs: Severe necrosis (N) and inflammatory infiltration (I). (C) AgNPs+MSE: Marked improvement with near-normal architecture.

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Kidney: The control and MSE groups showed intact glomeruli and renal tubules. The AgNPs group revealed severe tubular degeneration (TD), glomerular shrinkage (GS), and cast formation (C). These changes were markedly reduced in the AgNPs+MSE group, which displayed mostly preserved renal morphology (Figure 4).

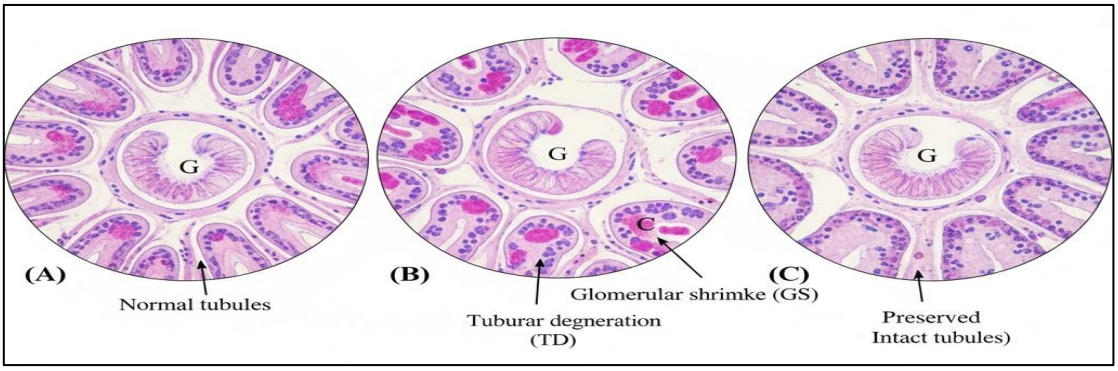

Figure 4: Photomicrographs of Kidney Sections (H&E, 400x).

(A) Control: Normal glomeruli (G) and tubules. (B) AgNPs: Tubular degeneration (TD) and cast formation (C). (C) AgNPs+MSE: Significant protection of renal structures.

3.4. Discussion

The observed hepatorenal toxicity in the present study aligns with the well-established paradigm that silver nanoparticle (AgNP)-induced damage is primarily mediated through oxidative stress mechanisms (Zhang et al., 2019). The accumulation of AgNPs in metabolically active tissues such as the liver and kidneys disrupts the mitochondrial electron transport chain, leading to an overproduction of reactive oxygen species (ROS). This oxidative burst depletes endogenous antioxidants, including glutathione (GSH) and superoxide dismutase (SOD), and induces lipid peroxidation, as evidenced by elevated malondialdehyde (MDA) levels. The resultant damage to cellular membranes and organelles is reflected in the elevated serum biomarkers of organ dysfunction and the observed histopathological alterations. The significant restoration of liver and kidney functional parameters, coupled with the amelioration of tissue morphology in the groups co-treated with *Moringa oleifera* seed extract (MSE), underscores its potent protective efficacy. This hepatorenal protection can be attributed to the high concentration of bioactive phytochemicals in MSE, such as flavonoids and phenolic compounds, which function as direct scavengers of free radicals, thereby preventing the initiation and propagation of the oxidative cascade (Leone et al., 2016; Tastan & Salem, 2021). Furthermore, specific phytoconstituents in *Moringa oleifera* are recognized for upregulating the expression and activity of key antioxidant enzymes like SOD and glutathione peroxidase (GPx), thereby enhancing the cellular defense system (Vongsak et al., 2013). This mechanism is consistent with the documented role of phytochemicals in aquaculture, where they mitigate oxidative stress by bolstering the innate defense systems of fish (Tastan & Salem, 2021). Our findings are further supported by studies on other medicinal plants, such as *Aloe vera* and *Vitex agnus-castus*, where dietary supplementation significantly improved antioxidant capacity, increased levels of protective enzymes, reduced lipid peroxidation, and enhanced hematological and immunological indices, leading to improved health and stress resistance (Salem, 2024; Salem et al., 2025). In conclusion, the efficacy of MSE in countering AgNP toxicity underscores the potential of leveraging the synergistic antioxidant and anti-

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inflammatory properties of phytochemicals as a strategic intervention against xenobiotic-induced oxidative stress.

4. Conclusion and Recommendations

In conclusion, this study provides compelling evidence that *Moringa oleifera* seed extract offers significant protection against AgNP-induced hepatorenal toxicity in mice. The primary mechanism of this protection is the attenuation of oxidative stress, as demonstrated by the normalization of MDA, GSH, and SOD levels. MSE effectively preserved the structural and functional integrity of the liver and kidneys.

Based on these findings, we recommend Further Research: Isolation and identification of the specific bioactive compound(s) in MSE responsible for the observed antioxidant and protective effects. Mechanistic Studies: Investigation into the molecular signaling pathways (e.g., Nrf2 pathway) involved in the upregulation of antioxidant enzymes by MSE. Applied Research: Exploration of MSE's potential as a protective adjuvant in industries where AgNP exposure is an occupational hazard, or as a supplement to mitigate the side effects of AgNP-based medical therapies.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

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