

RESEARCH ARTICLE

Editorial Process: Submission:01/06/2025 Acceptance:06/04/2025

Antioxidant property of Silver Nanoparticles Loaded with Alcoholic Extraction of Lycium Shawii

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Abstract

Background: Antioxidants play a crucial role in mitigating oxidative stress associated with cancer progression. Lycium shawii is noted for its high content of antioxidants and anti-inflammatory compounds. Silver nanoparticles (AgNPs) hold a prominent position among the various nanoparticles synthesized and characterized to date. **Objective:** In this study, we aimed to synthesize and characterize AgNPs loaded with alcoholic extracts of Lycium shawii and evaluate their antioxidant effects in vivo. **Methods:** Thirty rats were randomly divided into five groups, with six rats in each group. Group 1 (Control) was administered 1 mL of normal saline orally via a stomach tube daily. Group 2 received 1 mL of AgNPs at a dosage of 100 mg/kg on the day of administration. Group 3 was treated with 1 mL/day of Acetaminiprid at a dosage of 25 mg/kg. Group 4 was given AgNPs (100 mg/kg) for three weeks, followed by Acetaminiprid (25 mg/kg) for an additional three weeks. Group 5 received Acetaminiprid (25 mg/kg) for three weeks, followed by AgNPs (100 mg/kg). All treatments were administered daily, and serum levels of T-AOC, TOS, as well as the biomarkers AST, ALT, urea, and creatinine, were evaluated across all groups. **Results:** The results of the study demonstrated a significant increase in TOS, ALT, AST, urea, and creatinine, as well as a significant decrease in T-AOC ($p \leq 0.05$) in Group 3 compared to Groups 1, 2, 4, and 5. **Conclusion:** The in vivo results demonstrate that AgNPs, especially when combined with Lycium shawii extracts, exhibit significant antioxidant properties, suggesting a protective role against oxidative damage. These findings support the therapeutic potential of AgNPs in cancer treatment and oxidative stress-related disorders. Future studies are needed to fully elucidate the molecular mechanisms underlying the observed antioxidant effects and to assess the long-term safety and efficacy of AgNPs in clinical applications.

Keywords: Silver nanoparticles- lycium Shawii- cancer- antioxidant activity

Asian Pac J Cancer Prev, 26 (6), 2197-2204

Introduction

Antioxidants play a crucial role in combating oxidative stress associated with cancer development [1]. Cancer cells often exhibit elevated levels of reactive oxygen species (ROS), which contribute to oxidative stress. This oxidative stress can lead to DNA damage and mutations, thereby promoting tumorigenesis. Antioxidants can mitigate these effects by neutralizing ROS, thereby reducing the risk of cancer progression [2-5]. Medicinal plants and dietary supplements are recognized as valuable sources of food antioxidants. Antioxidants derived from natural food sources are generally regarded as safer than synthetic supplements. The interaction of dietary antioxidants with other nutrients can enhance their bioavailability and efficacy, making them more effective compared to isolated supplements [6]. Lycium shawii is rich in antioxidants, anti-inflammatory compounds, and antimicrobial or cytotoxic agents, making it a valuable resource for drug development and dietary supplements [7]. The active chemical compounds in plant extracts serve

as the primary basis for their pharmacological activities. Nanotechnology is a relatively new field in the modern world; however, materials with structural nanometer dimensions are not novel and have significant applications [8]. Nanotechnology offers innovative tools for developing more efficient and secure nanomedicines, presenting various potential benefits in drug formulation and delivery. It involves the engineering and industrialization of materials at the molecular and atomic scales [9, 10]. Currently, different procedures are used for the production of metallic nanoparticles, including biological, chemical, and physical methods. Mechanical milling and high-energy mechanical milling are effective physical methods for synthesizing nanoparticles (NPs). The chemical method typically involves the use of chemical substances for the preparation of NPs, which renders them unsuitable for various applications due to the inclusion of toxic compounds [11]. Among the various nanoparticles synthesized and characterized to date, silver nanoparticles (AgNPs) hold a prominent position, primarily due to their remarkable ability to act as antibacterial agents,

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even in solid form. Despite the long-standing recognition of silver's significance, its potential has largely been underutilized, with applications historically limited to coins and traditional medicine. Currently, approximately 320 tons of silver nanoparticles are produced annually, finding applications in food safety, biosensing, and nanomedical imaging [12]. Given the widespread use of silver nanoparticles, risk assessment of these nanoparticles is crucial, particularly in large-scale applications. Numerous studies have demonstrated the effectiveness of nanoparticles and their biological and cellular effects. However, an increase in reactive oxygen species (ROS) can lead to the breakdown of the antioxidant defense system, resulting in damage to DNA, lipids, and proteins [13]. Antioxidant systems consist of enzymatic and non-enzymatic components. Non-enzymatic antioxidants include water-soluble and membrane-bound molecules, such as ascorbic acid and glutathione. Antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX), play critical roles in defending against oxidative stress. Reduced glutathione, a sulfur-containing tripeptide, can either scavenge free radicals or act as a cofactor for GPX, which oxidizes glutathione-S-transferase (GST), thereby reducing the activity of SOD, the first line of defense against ROS. Previous research has shown that ROS acts as a biomarker for increased production and induction of oxidative stress, which can be altered by the activity of silver nanoparticles [14-16].

Acetamiprid, classified as a neonicotinoid insecticide, has the chemical formula $C_{10}H_{11}ClN_4$. It is an organic compound used to manage and control sucking insects that threaten a diverse range of crops, including leafy vegetables, fruiting vegetables, and cole crops. Acetamiprid is manufactured by Aventis CropScience and is commercially available under brand names such as Assail and Chipco [17]. The compound exerts its effects by binding to specific receptors within the synaptic cleft of nerve cells, thereby interfering with signal propagation in the insect's nervous system. Acetamiprid shares structural similarities with other neonicotinoids, such as imidacloprid, nitenpyram, and thiacloprid. It features a 6-chloro-3-pyridine methyl group, similar to these compounds, but differs in the substituent present on an acyclic or cyclic moiety, which may include nitroguanidine, nitromethylene, or cyanoamidine. Additionally, acetamiprid, structurally similar to nicotine, exhibits physiological effects comparable to nicotine in the human body. Nicotine, a naturally occurring insecticide, serves as the basis for synthesizing several synthetic insecticides [18, 19]. Acetamiprid is used in agriculture in various forms, such as wettable powders and water-soluble packs. It is essential to follow prescribed application instructions and safety measures to minimize potential risks to human health and the environment [20]. Furthermore, in this study we aimed to synthesize and characterize silver nanoparticles loaded with alcoholic extracts of *Lycium shawii* and evaluate their antioxidant effects *in vivo*.

Materials and Methods

Preparation of Extract from Lycium shawii

The *Lycium shawii* plant was collected from the outskirts of Diwaniyah. The leaves were thoroughly washed several times with plain water, followed by rinsing with distilled water to remove impurities. After washing, the leaves were shade-dried and ground into a fine powder using an electric mixer. The powder was then stored for future use. Subsequently, 20 grams of the crushed leaves were heated in 200 milliliters of filtered water at 45 °C for 30 minutes in a shaking water bath. After heating, the solution was wrapped in cellophane paper and left to stand for 24 hours before being filtered through filter paper [21].

Synthesis of Silver Nanoparticles

A mixture of 30 mL of 1 mM silver nitrate solution in water and 70 mL of the extract was prepared at room temperature with a pH of 8.5. The mixture was heated in a water bath and agitated at 45°C for 80 minutes to ensure thorough mixing. The appearance of a dark brown color indicated the formation of silver nanoparticles.

Experimental animals

The animals were acclimatized for two weeks prior to the experiments. Rats were divided into five groups, each consisting of six male rats (n=6). Group 1 (Control) received 1 mL of normal saline orally via a stomach tube daily. Group 2 received 1 mL of silver nanoparticles (AgNPs) at a dosage of 100 mg/kg on the day of administration. Group 3 was administered 1 mL/day of Acetamiprid at a dosage of 25 mg/kg. Group 4 received AgNPs (100 mg/kg) for three weeks, followed by Acetamiprid (25 mg/kg) for an additional three weeks. Group 5 was given Acetamiprid (25 mg/kg) for three weeks, followed by silver nanoparticles (100 mg/kg). All doses were administered daily, and serum levels of total antioxidant capacity (T-AOC) [22], total oxidant status (TOS) [23], AST, ALT [24], urea, and creatinine were assessed in all groups [25].

Statistical Analysis

The experiments were carried out three times, and the data shown comes from three separate trials. Statistical analysis was performed using Graph Pad Prism version 8.4.3, with results reported as mean \pm standard deviation (Mean \pm SD). A paired Student's t-test and one-way ANOVA were used to evaluate statistical significance, considering p-values less than 0.05 as statistically significant.

Results

UV-Vis Spectrum, SEM, and XRD analysis

Figure 1 illustrates the UV-Vis spectra results of silver nanoparticles in a 0.1 mM silver nitrate solution. Figure 2 presents the SEM micrographs of the synthesized silver nanoparticles. The Figure illustrates the irregular morphology and size of the synthesized nanoparticles, which were found to fall within the accepted nanoparticle size range of 1 to 100 nm.

X-ray diffraction (XRD) analysis was conducted to determine the size distribution and characteristics of the crystal structure. The results of the XRD analysis are presented in Figure 3.

Biochemical parameters

Table 1 shows the effects of green-synthesized silver nanoparticles on oxidative stress in male rats. Compared to the effects of N-[(6-chloro-3-pyridyl) methyl]-N'-cyano-N-methyl-acetamide, a chemical compound, the nature of its interaction with biological systems and the extent to which it contributes to oxidative stress remain unknown.

Table 2 shows the role of green-synthesized silver nanoparticles on liver enzymes in male rats. The results indicate a significant increase ($p \leq 0.05$) in ALT and AST enzyme levels in Group 3 (G3) compared to Groups 2

(G2), 4 (G4), and 5 (G5).

Kidney Function

As shown in Table 3, the levels of urea and creatinine increased in Group 3 (G3) compared to Groups 2 (G2), 4 (G4), and 5 (G5).

Histological Analysis of Liver and Kidney Tissues

After examining the histological slides of sections taken from the liver and kidney, the results of our study were consistent with the physiological findings, revealing pathological histological changes in the liver and kidney tissues.

Liver Tissue Analysis

Figure 4 presents various cross-sectional images of liver tissue. Image (A) depicts the control group,

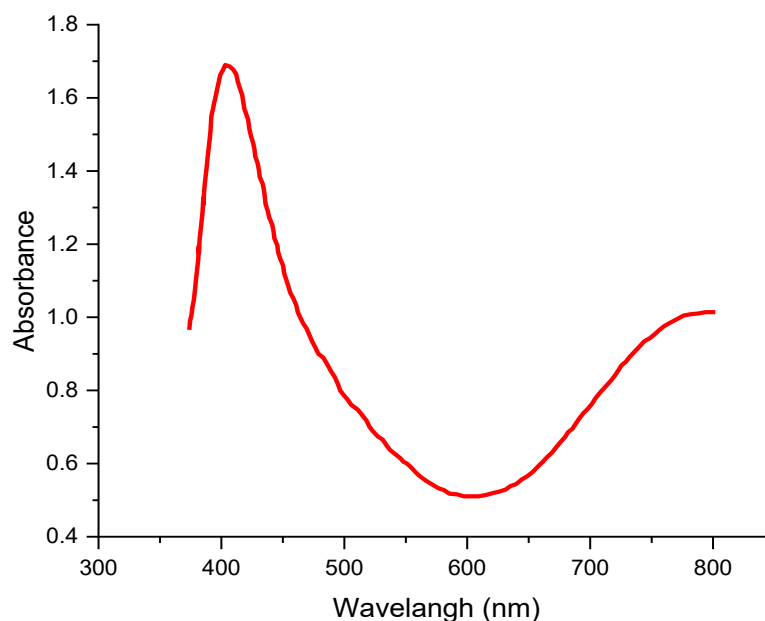


Figure 1. The Result of UV-Vis Spectra of Silver Nanoparticles in 0.1 mM Silver Nitrate Solution Concentration.

Table 1. The Effect of Green-Synthesized Silver Nanoparticles on Oxidative Stress Markers.

Oxidative stress			
T-AOC ($\mu\text{mol/L}$)		TOS ($\mu\text{mol/L}$)	
Mean \pm SD	P-value	Mean \pm SD	P-value
0.79 \pm 0.06	G1 & G2 = 0.67	1.75 \pm 0.44	G1 & G2 = 851
	G1 & G3 = 0.000*		G1 & G3 = 0.000*
	G1 & G4 = 0.000*		G1 & G4 = 0.000*
	G1 & G5 = 0.000*		G1 & G5 = 0.000
0.81 \pm 0.05	G2 & G3 = 0.000*	1.8 \pm 0.33	G2 & G3 = 0.000*
	G2 & G4 = 0.000*		G2 & G4 = 0.000*
	G2 & G5 = 0.000*		G2 & G5 = 0.000*
0.11 \pm 0.033	G3 & G4 = 0.61	4.54 \pm 0.55	G3 & G4 = 0.025*
	G3 & G5 = 0.013*		G3 & G5 = 0.003*
0.14 \pm 0.32	G4 & G5 = 0.04*	3.88 \pm 0.46	G4 & G5 = 0.353
0.244 \pm 0.129		3.62 \pm 0.31	

*Sing to difference significant at $P \leq 0.05$

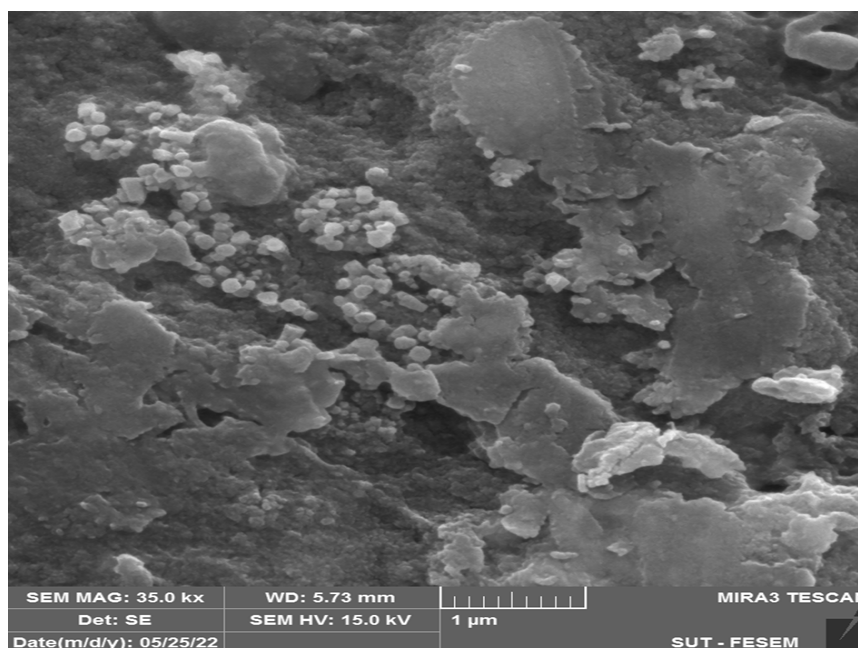


Figure 2. SEM Analysis of AgNPS Synthesised by Lycium Shawii.L. Plant Extraction

highlighting the central vein (yellow arrow), blood pockets (blue arrow), and hexagonal hepatocytes arranged in strands (red arrow). Image (B) shows the group treated with the extract, where similar features in the liver tissue are observed, including the central vein (yellow arrow), blood pockets (blue arrow), and hexagonal hepatocytes arranged in strands (red arrow). In images (C) and (D), which represent the group treated with acetaminophen, blood congestion in the central vein (yellow arrow) is noted, along with necrosis (indicated by other arrows) and the accumulation of inflammatory cells (black arrow). Image (E) illustrates the group treated with acetaminophen followed by the extract, revealing natural tissue characteristics, including the central vein (yellow arrow), blood pockets

(blue arrow), and hexagonal hepatocytes arranged in strands (red arrow). Finally, image (F) depicts the group treated with the extract followed by acetaminophen, where a slight expansion of the central vein (yellow arrow) and mild decay (blue arrow) are observed, while the hepatocytes appear normal and arranged in strands (red arrow).

Kidney Tissue Analysis

Figure 5 presents various cross-sections of kidney tissue from both control and treated group rats. Image (A) illustrates the kidney tissue of the control group, highlighting nearby urinary tubules (green arrow), distant urinary tubules (black arrow), glomeruli (blue arrow), and

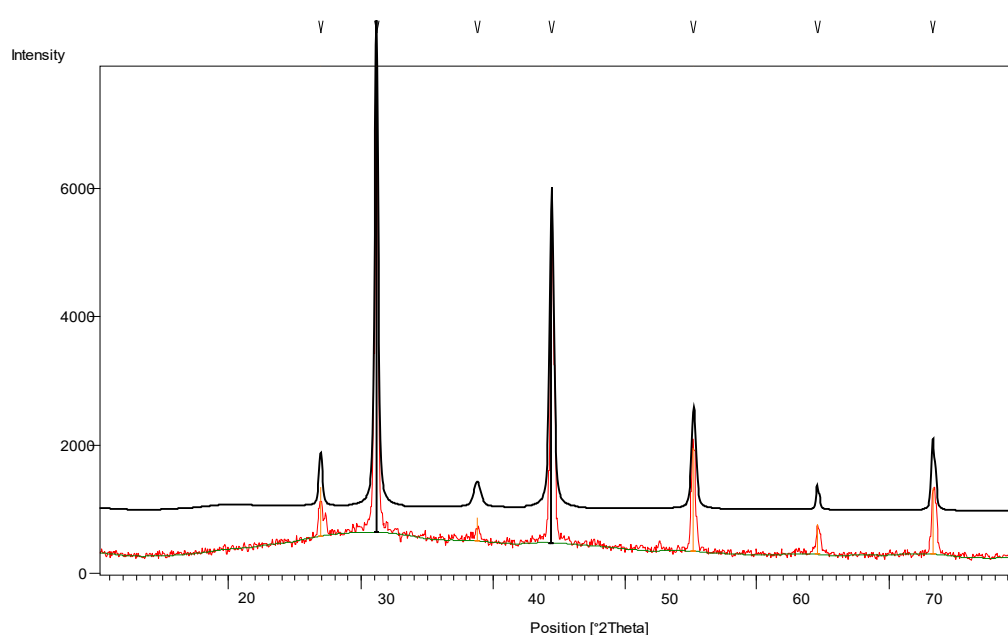


Figure 3. The XRD Analysis of AgNPS Synthesized by Lycium Shawii.L. plant Extraction

Table 2. The Effect of Green-Synthesized Silver Nanoparticles on Liver Enzymes Level

Group	Liver enzyme			
	ALT (U/L)		AST (U/L)	
	Mean \pm SD	P-value	Mean \pm SD	P-value
G1	30.4 \pm 1.67	G1 & G2 = 0.986 G1 & G3 = 0.000* G1 & G4 = 0.000* G1 & G5 = 0.000*	63.56 \pm 3.79	G1 & G2 = 0.725 G1 & G3 = 0.000* G1 & G4 = 0.000* G1 & G5 = 0.000*
G2	30.38 \pm 1.84	G2 & G3 = 0.000* G2 & G4 = 0.000* G2 & G5 = 0.000*	62.26 \pm 4.6	G2 & G3 = 0.000* G2 & G4 = 0.000* G2 & G5 = 0.000*
G3	59.76 \pm 1.17	G3 & G4 = 0.000* G3 & G5 = 0.000*	107.31 \pm 6.05	G3 & G4 = 0.129 G3& G5 =0.001*
G4	47.92 \pm 1.92	G4 & G5 = 0.001*	101.56 \pm 8.9	G4&G5 = 0.021*
G5	43.34 \pm 2.1		92.98 \pm 3.7	

*Sing to difference significant at $P \leq 0.05$

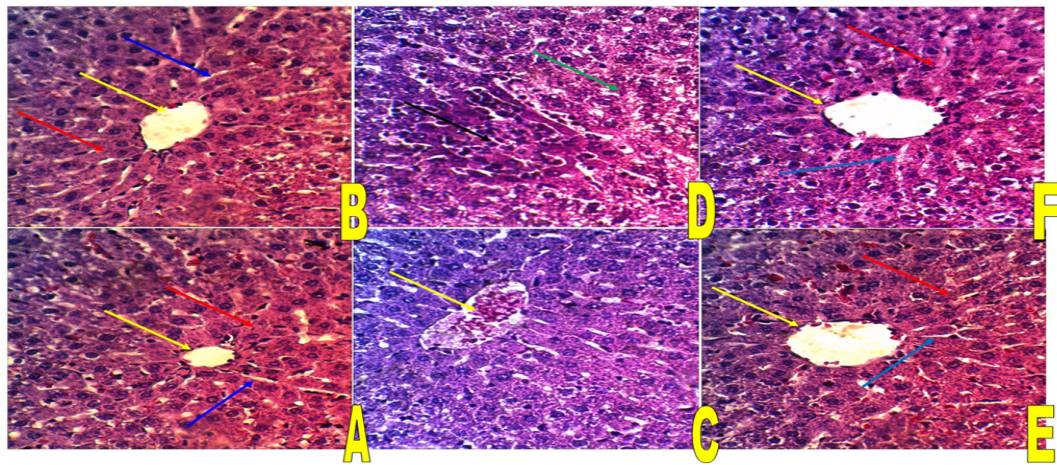


Figure 4. Histological Slides of the Sections taken from the Liver. (A): control group, (B): group treated with extract, (C and D): group treated with acetaminophen, (E): group received acetaminophen followed by extract, (F): group received extract followed by acetaminophen.

Bowman's capsule (yellow arrow). Image (B) depicts the kidney tissue of the group treated with the extract, showing

similar structures: nearby urinary tubules (green arrow), distant urinary tubules (black arrow), glomeruli (blue

Table 3. The Effect of Green-Synthesized Silver Nanoparticles on Kidney Function in Male Rats

Group	Kidney function			
	Urea (mg/dl)		Creatinine (mg/dl)	
	Mean \pm SD	P-value	Mean \pm SD	P-value
G1	6.63 \pm 0.41	G1 & G2 = 0.642 G1 & G3 = 0.000* G1 & G4 = 0.000* G1 & G5 = 0.001*	1.46 \pm 0.4	G1 & G2 = 0.786 G1 & G3 = 0.000* G1 & G4 = 0.000* G1 & G5 = 0.000*
G2	6.30 \pm 0.40	G2 & G3 = 0.000* G2 & G4 = 0.000* G2 & G5 = 0.000*	1.36 \pm 0.35	G2 & G3 = 0.000* G2 & G4 = 0.000* G2 & G5 = 0.000*
G3	16.32 \pm 2.06	G3 & G4 = 0.000* G3 & G5 = 0.000*	4.68 \pm 0.75	G3 & G4 = 0.04 * G3 & G5 = 0.01 *
G4	10.68 \pm 0.96	G4 & G5 = 0.56	3.88 \pm 0.55	G4 & G5 = 0.094
G5	9.26 \pm 0.76		3.24 \pm 0.72	

*Sing to difference significant at $P \leq 0.05$

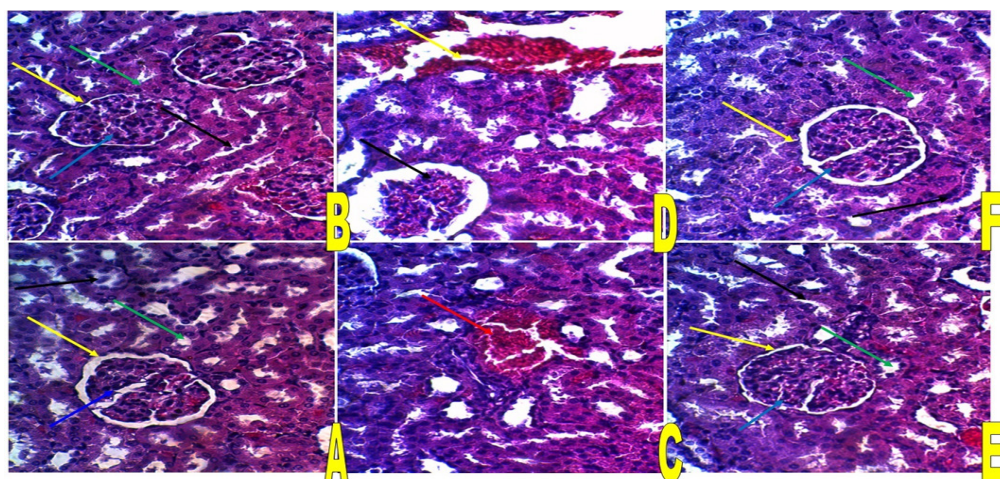


Figure 5. Histological Slides of the Sections Taken from the Kidney. (A): control group, (B): group treated with extract, (C and D): group treated with acetaminophen, (E): group received acetaminophen followed by extract, (F): group received extract followed by acetaminophen.

arrow), and Bowman's capsule (yellow arrow). Images (C) and (D) display cross-sections of kidney tissue from the group treated with acetaminophen, where atrophy in the glomeruli (black arrow), blood congestion (red arrow), and bleeding (yellow arrow) are observed. Image (E) shows a cross-section of kidney tissue from the group treated with both acetaminophen and the extract, revealing natural tissue with nearby urinary epithelium (green arrow), distant urinary tubules (black arrow), glomeruli (blue arrow), and Bowman's capsule (yellow arrow). Finally, Image (F) presents a cross-section of kidney tissue from the group treated with the extract followed by acetaminophen, where a slight expansion of Bowman's capsule (yellow arrow), mild atrophy in the glomeruli (blue arrow), and expansion of distant urinary tubules (black arrow) are noted.

Discussion

The homogenized extract demonstrated superior nanoparticle production in the synthesis of silver nanoparticles from the *Lycium shawii* L. plant extract. The reaction environment confirmed the presence of silver nanoparticles. Due to surface plasmon resonance, the color of the reaction medium gradually changed to dark brown. The surface plasmon band is influenced by factors such as the dielectric environment, morphology, size, composition, and shape of the nanoparticles. The degree of absorption increased with the synthesis of more silver nanoparticles, as indicated by previous research [26]. The visible range of UV spectra for silver nanoparticles (AgNPs) typically falls between 410 and 500 nm, while the absorption in this study ranged from 420 to 450 nm. The scanning electron microscope (SEM) has enhanced our understanding of the morphological characteristics of the *Lycium shawii* L. plant, from which silver nanoparticles (AgNPs) were synthesized. Figure 2 presents the SEM micrographs of the synthesized silver nanoparticles [27]. The Figure illustrates the irregular morphology and size of the synthesized nanoparticles,

which were found to fall within the accepted nanoparticle size range of 1 to 100 nm.

Different chemical substances may exert varying impacts on oxidative stress, depending on their mechanisms of action and concentrations. In the absence of specific data or studies on this particular compound, we can only provide general insights into how chemical compounds might be associated with oxidative stress [28]. Substances can act as either pro-oxidants, which contribute to oxidative stress by generating reactive oxygen species (ROS), or antioxidants, which mitigate oxidative stress by scavenging ROS. The characteristics of N-[(6-chloro-3-pyridyl) methyl] warrant further investigation. The role of N'-cyano-N-methyl-acetamidine in this context requires experimental exploration, as there is a possibility that this substance may negatively affect enzymes and proteins, thereby leading to oxidative stress [29, 30]. Studies have demonstrated that the antioxidant properties of silver nanoparticles (AgNPs) inhibit free radicals and reduce oxidative stress. The ability of AgNPs to donate electrons and neutralize reactive oxygen species (ROS) is well-documented [31]. AgNPs contain natural antioxidants, such as vitamins C and E, and their combination with these antioxidants may offer enhanced protection against oxidative damage. AgNPs have been utilized in biomedical applications, particularly in drug delivery systems, where they can transport and release antioxidants at targeted sites within the body. This approach improves the bioavailability and efficacy of antioxidants. While AgNPs exhibit antioxidant properties, it is crucial to recognize that they can also demonstrate cytotoxic effects, particularly at elevated concentrations. The balance between their antioxidant benefits and potential toxicity requires careful consideration in various applications. In some cases, AgNPs are coated with antioxidant compounds to enhance their stability and mitigate potential toxicity. This combination may provide a safer and more effective platform for diverse applications. Ongoing research is exploring the use of AgNPs in the development of new

antioxidant-based therapies and materials, including their incorporation into wound dressings, food packaging, and cosmetic products to extend shelf life and improve product quality. In summary, the relationship between AgNPs and antioxidants is complex. While AgNPs can exhibit antioxidant properties, they are also used alongside antioxidants in various applications, potentially amplifying the overall antioxidant effect. However, their use must be carefully regulated and assessed to ensure safety and efficacy in specific contexts [32].

The elevation in the ALT and AST Levels may be attributed to cell death mechanisms associated with acetamiprid consumption in rats, which generates reactive metabolites and free radicals due to oxidative stress and degradation processes. These factors contribute to increased levels of ALT and AST. Typically, these enzymes are detoxified through conjugation with glutathione (GSH). However, in cases of overdose, the availability of GSH becomes limited, leading to liver damage, including mitochondrial impairment, oxidative stress, and nuclear DNA fragmentation [33]. Conversely, the decrease in AST and ALT enzyme levels in groups treated with silver nanoparticles may be attributed to the role of AgNPs in mitigating damage caused by free radicals or protecting tissues from adverse changes. Additionally, these nanoparticles may enhance the activity of enzymes responsible for detoxification [34].

This increase in the urea and creatinine levels are attributed to disturbances in kidney function caused by the effects of pesticides. These disturbances disrupt metabolic processes through the production of toxic compounds, ultimately affecting tissues [35]. Elevated levels of urea and creatinine can be detrimental to tissue health and negatively impact kidney function. The increase in urea and creatinine levels may result from the harmful effects of acetamiprid consumption, which can cause oxidative stress and damage to kidney tissue. Alternatively, this elevation may be due to a reduced glomerular filtration rate, caused by increased resistance in the glomerular arterioles or a decrease in blood volume, both of which can impair creatinine excretion and lead to its accumulation in the body [36]. The observed improvement and decrease in urea and creatinine concentrations in Groups 4 (G4) and 5 (G5) may be attributed to the role of nanosilver as a potent antioxidant. Nanosilver appears to protect cell membranes from the detrimental effects of free radicals, thereby promoting kidney function and maintaining the glomerular filtration rate within the normal range [37].

In summary, the findings of this study underscore the promising potential of silver nanoparticles loaded with alcoholic extracts of *Lycium Shawii* as effective antioxidant agents. The *in vivo* analysis revealed that AgNPs, particularly when combined with the bioactive components of *Lycium Shawii*, demonstrated substantial antioxidant activity, successfully modulating oxidative stress markers and providing protection against oxidative damage. While exposure to Acetamiprid induced significant oxidative stress, as evidenced by elevated levels of oxidative stress markers and biomarkers such as TOS, ALT, AST, urea, and creatinine, the treatment with AgNPs alleviated these effects, suggesting a protective role of

AgNPs against oxidative damage. This study highlights the therapeutic potential of AgNPs as a viable intervention for oxidative stress-related disorders, including cancer. However, additional research is needed to delve deeper into the molecular mechanisms behind the observed antioxidant effects, as well as to assess the long-term safety and efficacy of AgNPs in clinical settings. These findings provide a strong foundation for further investigation into the role of silver nanoparticles in drug development and their potential as dietary supplements

Author Contribution Statement

Meaad Nasser Hussein and Yusra Sebri abdulsaheb: Methodology, Investigation, Data curation, Original draft preparation.

Ali NooryFajer: Supervision, Conceptualization, Writing- Reviewing and Editing.

Acknowledgements

Availability of data and materials

The data and materials that support the findings of this study are available from the corresponding author, upon reasonable request.

Ethical Approval

This research protocol was evaluated and approved by Researches Ethics Committee of AL-Qadisiyah University, Iraq.

Conflict of interest

The authors declare that they have no conflict of interests.

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