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DEVELOPING EFFECTIVE STRATEGIES AND INNOVATIONS TARGETING THE SCABIES PARASITE (SARCOPTES SCABIEI)

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Abstract
Scabies, caused by the scabies mite *Sarcoptes scabiei*, is a major global health challenge due to limited treatment options and increasing parasite resistance. Ag_2O NPs were prepared using an environmentally friendly green manufacturing method that utilized three extracts: *lemon peel* oil, *aloe vera* gel, and *colocynth seed* extract. Their efficacy against scabies in BALB/c mice was investigated. The nanoparticle formulations were used to treat 60 infected mice, divided into groups, and their efficacy was compared to that of the acaricide benzyl benzoate. LO-Ag_2O Nps demonstrated the highest efficacy in eliminating the parasites, and quantitative polymerase chain reaction (qPCR) results showed a significant increase in the cycle threshold (C_t) value ≥ 35 in the treated mouse group. This is consistent with histological examination, which revealed significant skin healing, and microscopic examination of skin scrapings, which showed no parasites. qPCR results for both (CC-Ag_2O and AV-Ag_2O) NPs samples groups resulting in a (C_t) of less than 35, indicating a lower percentage reduction in parasites compared to LO-Ag_2O and benzyl benzoate. This was further confirmed by microscopic examination and histological examination, which revealed the absence of the parasite in LO-Ag_2O and benzyl benzoate. These results highlight the potential of plant derived Ag_2O NPs formulations as safe and effective alternatives to conventional acaricides, and thus their use in initiating scabies control programs in resource limited settings.

1. Introduction

The Latin word "scabere" is the source of the scientific name for the mange parasite (*Sarcoptes scabiei*) (Arlian & Morgan, 2019). It is an ectoparasite that infects many mammalian species. It has characteristic skin symptoms that may include a rash in the form of nodules, as well as intense itching that usually worsens at night (Bernigaud *et al*., 2020). The parasites, which are generally almost invisible, mostly live-in burrows on less furred skin areas, including ears, tail, and limbs, where they do not colonize hair follicles (Sunderkötter *et al*., 2016). Transmission is mainly through direct contact as the parasite can only survive off-host for 24–36 hours, limiting indirect infection with fomites such as bedding (Walton & Currie, 2007). Adult parasites find new hosts mainly through odor signals and thermotaxis (Arlian & Morgan, 2019). Morphologically, parasites derived from skin nodules have sac-shaped bodies; the tarsi of the first two pairs of legs have pedicellate (stalked) ambulacral discs or spines. Female parasites have a transverse slit for the genital opening without the epigynum and genital suckers. Their tarsi lack apical claws but include modified stout spine-like setae; dorsal body striae consist of strong serrated spines. Posterior body setae are lance-shaped, robust, and short; the anus is terminal (Fain, 1968). Such characteristics support the diagnosis of the parasite as a *Sarcoptes* species, a genus responsible for the etiology of scabies mange in mammals, such as mice (Bornstein et al., 2001), as shown in Figure 1.

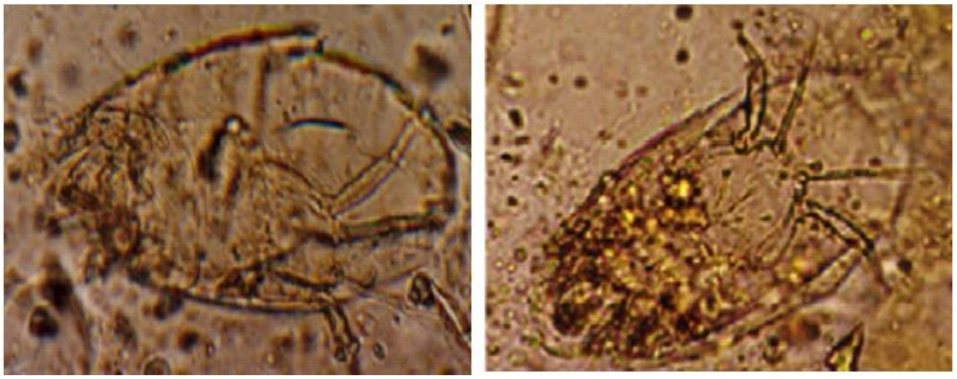


Figure 1: *S. scabiei* parasite isolated from skin lesions in laboratory mice (Diagnosis: Sarcoptic mange, 2007).

The clinical appearance can be mistaken for other itchy skin conditions such as eczema or fungal infections (Walton & Currie, 2007). This parasite is widespread globally among rodents and many other animals, prompting researchers to search for therapeutic agents to kill or inhibit the parasite (Mounsey *et al*., 2008). A study is underway to develop environmentally friendly and biocompatible nano therapies, which represent a new approach to their preparation where plant compounds are used to enhance the provision of long-term protection against the scabies parasite *S. scabiei* (Ahmed *et al*., 2024; Benelli, 2018a). Current treatments for Scabies in mice rely on limited therapies, which suffer from constraints related to resistance development, safety, and efficacy. Permethrin, a pyrethroid available as a 5% topical cream, is the safest and most effective treatment. Permethrin acts directly on the nervous system of the parasite *S. scabiei* , leading to paralysis and death (Cochi & Heukelbach, 2022). Repeated use of permethrin may lead to the emergence of resistant strains of the parasite, raising concerns about its long-term efficacy (Pasay *et al*., 2008). Ivermectin is administered orally or topically at a dose of 200 µg/kg, and treatment is repeated after 7–14 days if no live mites or eggs are observed (Mounsey *et al*., 2016). Ivermectin achieves cure rates of approximately 97% in mice under optimal conditions (Chhaiya *et al*., 2012). Benzyl benzoate, a commonly used treatment for scabies, is available as a 25% w/v solution. It is usually applied directly to affected skin areas to treat sarcoptic and human scabies. Despite its proven efficacy, severe skin irritation or burning can occur during application, leading to its avoidance and highlighting the need for safer alternatives (Meyersburg *et al*., 2024). Nanotherapies generally exhibit remarkable properties due to their antagonistic effect on the physiological processes of the scabies mite *S. scabiei* . They inhibit the biosynthesis of ecdysone, a hormone essential for mite molting and growth, thus halting their development and leading to their death (Alinezhad *et al*., 2021; Pavela & Benelli, 2016). These therapies also directly inhibit cytochrome P450 monooxygenase enzymes, which are involved in the parasite's detoxification processes, thereby suppressing the metabolism of foreign substances and contributing to the reduction of resistance development (Benelli, 2018a; Feyereisen, 2012). Due to the increasing resistance of the host parasite to commercial chemical treatments, this may play a significant role in the deterioration of the health of infected organisms, particularly those infected with *S. scabiei* . This has spurred the development of novel therapeutic strategies, including the environmentally friendly preparation of silver oxide nanoparticles using plants. The resulting product is silver oxide nanoparticles coated with biomaterials extracted from the plant used in the preparation process.

2. Materials and Methods

2.1 Preparation of plant extracts

- *Aloe Vera* gel (AV): Preparing 100% pure raw gel requires following specific protocols consisting of several steps. The first step begins by collecting fresh aloe vera leaves from the gardens of Wasit University. These leaves are cut and left vertically for 20 minutes to remove aloin, a toxic laxative substance (Anwar *et al*., 2021). The leaves are then washed to remove impurities and salts and rinsed thoroughly with pure distilled water. This process produces clean peels, after which the green peel is discarded, leaving a clear gel that is then cut (Ramachandran *et al*., 2020). The pieces are placed in a piece of cloth, preferably cotton, to form a gel filter. After obtaining the gel filter, it is placed in sterile tubes in a centrifuge and run at 4000 rpm for half an hour. This process is repeated twice to ensure that the extract does not overheat, in order to remove impurities (Anwar et al., 2021; Ramachandran *et al*., 2020).

- *Citrus limon* (L.) Osbeck peel essential oil (LO): *Lemon peel*s were collected from Iraqi lemons harvested on private farms in Kut, Wasit Governorate. To obtain essential oil, a Clevenger apparatus was used for hydrodistillation for three hours (Boughendjioua & Boughendjioua, 2017). Anhydrous sodium sulfate was used to remove residual moisture, and to maintain 100% essential oil quality, it was stored at 4°C (Benelli *et al*., 2017; Khamhaengpol & Suttisawat, 2022).

- Extract of *Citrullus colocynthis* seeds (CC): The seeds of colocynth (*Citrullus colocynthis*) are extracted from the fruit of this plant in the Nukhaib Desert of Anbar Governorate, Iraq. After collection, the seeds are thoroughly washed with distilled water to remove impurities and then air-dried at 25°C for approximately one week. The seeds are then ground into a powder using an electric mill in the laboratory, and the powder is added to a 70% ethanol solvent. The mixture is infused at a 1:10 (w/v) ratio with intermittent shaking at room temperature for 48 hours (Hussain *et al*., 2014). The extract is then filtered to remove impurities. The extract is heated to 50°C under reduced pressure using a rotary evaporator, resulting in a dry crude extract. A 10% (w/v) alcoholic extract is then prepared (Hussain *et al*., 2014).

2.2 Synthesis of Ag_2O NPs

To prepare Ag_2O particles, the plant extracts mentioned previously are prepared (Ramachandran *et al*., 2020; Khamhaengpol & Suttisawat, 2022; Gurudeeban *et al*., 2011). Each extract is added separately after preparing 100 ml of deionized water and adding silver nitrate to obtain a concentration of 10 mM (Khamhaengpol & Suttisawat, 2022). Then 25 ml of plant extract is added, and a mechanical stirring motor is used for mixing for 120 min at a temperature of 85 °C. After that, the mixture is placed in sterile 10 ml tubes and placed in a centrifuge for a period of 15 minutes at a speed of 4,000 rpm. The mixture is washed with deionized water and returned to the centrifuge. This process is repeated until a neutral pH of 7 is obtained for the mixture. The precipitate is obtained, dried, and ground. Then it is placed in an oven at a temperature of 200°C for a period of 60 min (calcination) to facilitate the preparation of capped silver oxide nanoparticles with plant extracts (Ahmed *et al*., 2024; Khamhaengpol & Suttisawat, 2022). Each sample of Ag_2O NPs prepared using the plant extract was coded respectively as follows (AV-Ag_2O, LO-Ag_2O and CC-Ag_2O) NPs.

2.3. Detection of *S. scabiei* by TaqMan Real-Time PCR:

To evaluate the density of the mange-causing parasite in groups of infected mice after treatment with silver oxide (AV-Ag_2O, LO-Ag_2O, and CC-Ag_2O) NPs and benzyl benzoate, the next steps:

2.3.1. DNA Extraction:

The genomic DNA was extracted from *S. scabiei* by using Wizard genomic DNA kit (GENAID). This kit allows efficient extraction of DNA with high yield and purity. The extracted DNA is suitable for downstream applications such as conventional PCR, real-time PCR, sequencing, and genotyping of *S. scabiei* . The purity of the extracted DNA were verified via Nanodrop spectrophotometry prior to storage at -20°C.

2.3.2. TaqMan Real-Time PCR:

To detect *S. scabiei* using TaqMan Real-Time PCR, the target was highly conserved mitochondrial gene (cox1) by using specific primer as the following: Forward Primer 5′-TGATTTTTTGGTCATCCTGAAGTT-3′, Reverse Primer 5′- ACACCAATTCCAAATCCTAATAAA-3′ and TaqMan Probe 5′-[FAM]- TTTTTTAGTTTTCGTTTCTGCTGGAGC -[BHQ1]-3′ .The reactions were conducted in a 20µL reaction mixture containing 10µL of TaqMan probe Master Mix, 1µL of each specific primer and probe (10µM), 2µL of DNA template, and (5 µL) of nuclease-free water. The thermocyclar program consisted of an initial denaturation at 95°C for 5 min, followed by 40 cycles of denaturation at 95°C for 30 S and annealing/extension at (60°C) for 1 min, with simultaneous fluorescence detection. To ensure analytical consistency, the threshold line was uniformly set at 0.50 to determine cycle threshold C_t values and construct amplification.

3. Nanoparticle Characterization

Three silver oxide nanoparticle samples were prepared in the laboratories of the College of Science, Wasit University. The properties of these particles were then examined at the central laboratory of Tehran University to determine their suitability for killing the scabies mite and inhibiting its growth. To achieve this, the following analyses were performed:

- As shown in Figure 2, X-ray diffraction (XRD) analysis was performed, and it was found that the structure of all samples is cubic and is highly consistent with COD cards 96-431-8189 and 96-901-2962, respectively.

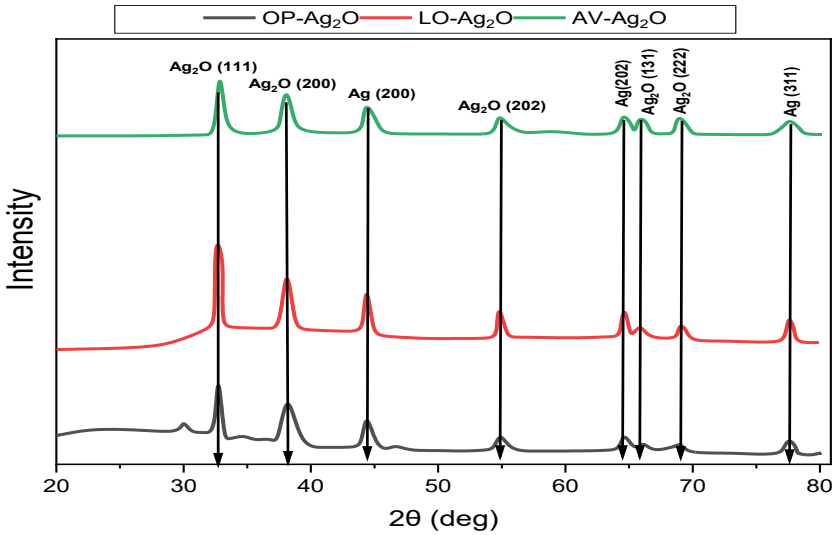
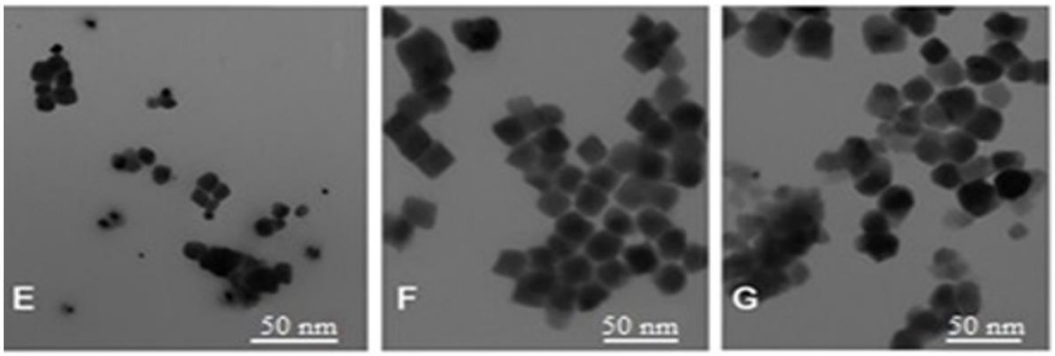


Figure 2: X-ray diffraction (XRD) patterns of silver oxide nanoparticles prepared by green synthesis.

- Following analysis of the Ag_2O NPs samples using the JEOL JEM-2100 TEM, it was determined that the nanoparticles were characterized by a highly homogeneous distribution and spherical shape, as shown in the Figure 3.



LO-Ag_2ONPs average particle size of 40 ± 3 nm. CC-Ag_2ONPs average particle size of 67 ± 4 nm. AV- Ag_2ONPs average particle size of 68 ± 3 nm.

Figure. 3: Images transmission electron microscopy (TEM) of Ag_2O NPs.

4. In Vivo Treatment Protocols

This experiment was conducted in the animal house at Wasit University and the laboratories of the College of Science, the Department of Biology. The effect of Ag_2O NPs prepared by green synthesis methods against *S. scabiei* infection in BALB/c mice was reported in treatment experiments compared to a standard chemical control in vivo. BALB/c mice weighing (25-30) g were obtained from a certified breeder and were tested for infection with *S. scabiei* , clinically diagnosed by pruritus and erythema and verified by microscopy of scrapings at 40x magnification (Arlian & Morgan, 2019; Walton & Currie, 2007)

The 0.3 ml volume for topical application in rodents was determined based on several factors, most importantly the surface area of the affected skin in the mice, taking into account the need to avoid leakage and systemic toxicity of the treatment (Burkhart *et al.*, 2001; Diehl et al., 2001), in addition to laboratory animal dosing guidelines (OECD, 2021).

The mice were randomly distributed into five groups of 12 animals each, with three treatment groups treated with prepared Ag_2O NPs; one chemical control group was Benzyl benzoate, a known treatment for mange mites, was tested topically on twelve infected mice. It was used at a concentration of 25% w/v. A 0.3 ml dose was administered to the affected area of skin for seven consecutive days. Skin scrapings were taken on days 0, 7, 14, and 21 to assess treatment efficacy, and one negative control group was treated with distilled water (Sunderkötter *et al*., 2016). Treatments were implemented in affected areas, such as the ears, tail, and limbs, based on established environmental conditions (22°C temperature, 60% relative humidity, 12h light/dark cycle) with ad libitum water and chow.

Clinical signs, which indicate the causative activity of the *S. scabiei* , were identified as the primary cause of itching and can be assessed on a scale of 0 to 4. Skin scrapings were taken to identify scabies parasites *S. scabiei* using a 40x magnification microscope. This was done to determine the infection and recovery rates, and to assess the disappearance of clinical symptoms in mice due to the effectiveness of both conventional treatments and the bio-prepared silver oxide nanoparticles.

5. Results and Discussion

Microscopic examination of skin scrapings showed that all three synthesized nanoparticle formulations exhibited significant therapeutic efficacy. Scrapes collected post treatment on days 0, 7, and 14 showed a significant decline in parasite numbers to varying degrees. After treatment on day 21, the LO-Ag_2O NPs sample showed complete eradication of the parasites and resolution of all clinical symptoms, a result consistent with benzyl benzoate treatment. In contrast, the other formulated samples induced (CC-Ag_2O and AV-Ag_2O) NPs only a partial significant decline in the parasitic load, suggesting incomplete parasite clearance.

Microscopic examination revealed the absence of parasites but the presence of eggs and larvae, indicating significant decline rather than elimination. Comparative photographs of skin lesions before and after treatment were documented in Figure 5. Histopathological evaluation confirmed these findings: in the group treated with LO-Ag_2O NPs, the dermis and epidermis appeared almost normal with a mild inflammatory response after 14 consecutive days of topical application (0.3 mL, 25% v/v) Figure 4a. Similarly, mice treated with LO-Ag_2O NPs showed structural skin recovery, characterized by minimal infiltration of inflammatory cells after 14 days of daily topical treatment 0.3 mL, indicating continued tissue repair and reduced lesion severity Figure 4b. In contrast, the untreated control group exhibited extensive epidermal destruction and vascular congestion on day 0 this sample was taken from a mouse infected with the parasite in the control group Figure 4C, with histological sections revealing infiltrating mites consistent with active infection and tissue damage Figure 4D.

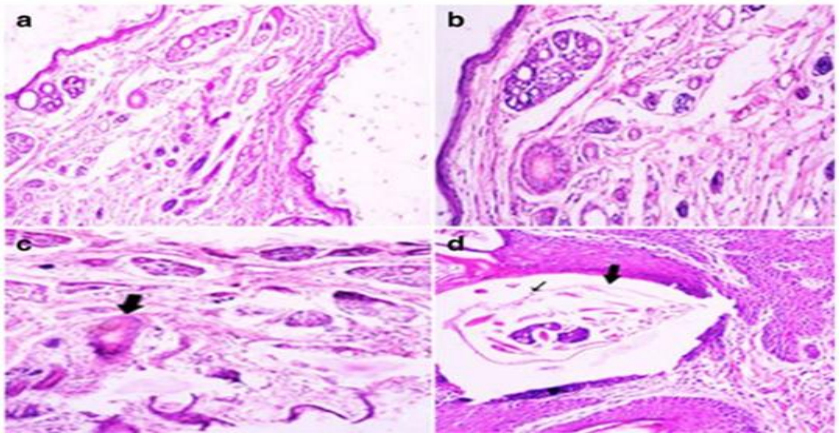


Figure 4: Histopathological examination of mice infected with *S. scabiei* .

Quantitative polymerase chain reaction (qPCR) testing was performed to confirm the microscopic and histological findings. The results showed a significant increase in $C_t \geq 35$ threshold values in the group of mice treated with LO-Ag_2O NPs. This indicates the absence of *S. scabiei* DNA in the measured sample, which is consistent with previous tests as shown in Figure 4, suggesting the end of the parasite's life cycle. LO-Ag_2O NPs are considered an effective treatment comparable to the antiscabietic agent benzyl benzoate. The results were positive, with the parasite disappearing in the group treated with this therapy, as confirmed by microscopic examination on day 21 (Meyersburg *et*

al., 2024). Their similarity in action is particularly evident in the eradication of the *S. scabiei* . This performance is distinguished by the compatibility of plant-based organic compounds with silver oxide, making it a promising alternative to acaricides.

Recent research is consistent with the efficacy of Ag_2O NPs, which are also investigating alternative treatments for *S. scabiei* . For example, Ahmed *et al*. (2024) demonstrated the use of silver and gold nanoparticles as an innovative therapeutic intervention for scabies in rabbits. As in other areas, the increasing resistance of parasites to conventional compounds is the driving force behind the development of these nano alternatives (Wróblewski *et al*., 2024). Their results support published findings and confirm the promising therapeutic potential of silver based nanoparticles against the scabies mite (Ahmed *et al*., 2024; Zhang *et al*., 2023). The (CC-Ag_2O and AV-Ag_2O) NPs mouse groups show a higher concentration of parasite DNA, resulting in a $C_t < 35$, as shown in table 1. Microscopic examination showed the absence of adult stages, while eggs and larvae remained relatively few. It is important to note that these treatments developed for these samples are primarily aimed at alleviating symptoms and do not have the ability to completely eradicate the parasite as happened with the LO-Ag_2O NPs mouse group.

Table 1: Quantitative detection of *S. scabiei* DNA in mice.

Evaluation Group	$C_t \pm SD$	*S. scabiei* detection	Calculated Anti-*S. scabiei* Efficacy %
AV-Ag_2O NPs	26.12 ± 0.35	positive (+)	90.24%
CC-Ag_2O NPs	27.14 ± 0.42	positive (+)	90.54%
LO-Ag_2O NPs	36.18 ± 0.16	Negative (-)	> 99.99 %
Benzyl benzoate	36.12 ± 0.23	Negative (-)	> 99.99 %
Control	19.18 ± 0.32	positive (+)	0.0 %

These Ag_2O NPs, produced using green synthesis, play a significant role in eliminating the *S. scabiei* parasite through a number of integrated pathways that work together to destroy the mite and its eggs. The most important mechanism of killing this parasite is cellular oxidative stress. The size of the particles helps in penetrating the parasite; the smaller the size of the nanoparticles, the greater the amount of penetration they contribute to, this contributes to the production of ROS such as peroxides and superoxide radicals. These, in turn, exceed the parasite's ability to resist them through natural antioxidant defenses (Abdel-Rahman *et al*., 2022; Khan *et al*., 2021).

These resulting free radicals have a role in attacking the fatty acids that make up cell membranes lipid peroxidation after they are penetrated by silver nanoparticles. This can lead to holes in the membrane and a sudden leakage of fluids from the cell (Gurunathan *et al*., 2019). Ag_2O NPs have the ability to produce released silver ions Ag^+ that have the ability to enter the nucleus and bind to nitrogenous bases, which contributes to the destruction of DNA and inhibition of the replication enzyme (Zhang *et al*., 2023). This is consistent with the absence of the parasite's genetic material in the qPCR assay of the LO-Ag_2O NPs treated group and the high $C_t \geq 35$. The reason for the superiority of this treatment over the rest is due to the small particle size of 40 nanometers. As for the two therapeutic models, (CC-Ag_2O and AV-Ag_2O) NPs, they lack the ability to completely eradicate the parasite due to their large nanoparticle sizes 67 and 68 nm, respectively. These sizes indicate limited penetration of the parasite in small quantities, thus reducing oxidative stress and the production of Ag^+ and ROS (Benelli, 2018b). This is consistent with the qPCR examination of the treated group and the decrease in the threshold value $C_t < 35$, in which symptoms appear mild, larvae and eggs appear in the microscopic examination.

6. Conclusion

The biosynthesized samples demonstrated high efficacy against the scabies mite. The results showed a marked superiority of these samples in killing the mites and inhibiting their growth. Clinical results also demonstrated a cure rate comparable to and exceeding that of benzyl benzoate treatment, as shown in the group of mice treated with LO-Ag_2O NPs. These biosynthesized silver oxide samples have proven to be important therapeutic agents against this mite, opening the door to controlling its spread and developing a treatment that may be available in the future.

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