Research Article

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Synthesis and characterization of noble metal/metal oxide nanoparticles and their potential antidiabetic effect on biochemical parameters and wound healing

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Abstract: The study assessed the antidiabetic effect of *Solenostemma argel* and its nanoformulations with silver/gold nanocomposites (CNPs), zinc oxide nanoparticles (ZnONPs), and metformin drug. Experimental groups consisted of normal control, diabetic control, and four diabetic groups treated with metformin, CNPs, ZnONPs, and bulk argel leaf extract (So-argel). Transmission electron microscopy characterization showed that the synthesized CNPs and ZnONPs were of variable sizes and dimensions and were quasi-spherical in shape. Particle sizes measured by dynamic light scattering were 106 and 139 nm for CNPs and ZnONPs, respectively. Also, the polydispersity index values were 0.473 and 0.269 for CNPs and ZnONPs, respectively. The biochemical parameters were as follows: the

group treated with bulk So-argel ($105.00 \pm 4.041 \text{ mg-dL}^{-1}$) and CNPs ($109.00 \pm 8.373 \text{ mg-dL}^{-1}$) showed a more profound anti-hyperglycemic effect and were comparable to the control (88.40 ± 2.249). Liver and kidney functions ($p \leq 0.05$) improved with So-argel and its nanoformulations compared to metformin. However, bulk argel (170.33 ± 20.431 and $38.00 \pm 3.05 \text{ U-L}^{-1}$) and the nanocomposite (228.33 ± 11.464 and $48.00 \pm 5.291 \text{ U-L}^{-1}$) were efficacious in lowering serum levels of liver enzymes (AST and ALT, respectively). No significant difference was observed between urea levels. Nevertheless, bulk So-argel (0.26 ± 0.007) and CNPs (0.24 ± 0.018) were more effective than ZnONPs (0.41 ± 0.289) on serum creatinine. Nanotreatment exhibited a reduction in lesions size/healing. Overall, nanoparticles may offer a safe potential for Type 2 diabetes management.

Keywords: a diabetic lesion, diabetes mellitus, nanoparticles, *Solenostemma argel*

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1 Introduction

Diabetes mellitus is one of the predominant ‘diseases of civilization’, which is globally prevalent and affects a vast section of the human population. Diabetes rates are still high and continue to be a challenge for the global health care systems. The estimated projected value is 592 million by 2040 [1]. The disease (both Type 1 and Type 2) is mainly considered by insulin reduced secretion or insulin resistance, hence, causing a marked alteration in carbohydrate levels, fat and protein processing, as well as an elevation in serum glucose levels [2]. The associated long-term health complications in diabetes include cardiovascular risks, nephropathy, liver disorders, and neuropathy, which is nerve damage throughout the body, particularly the limbs. Consequently, it causes diabetic

lesions (such as foot and leg ulcers), which harmfully affects wound healing by reducing the flow of blood and oxygen to the infected area. Moreover, it results in a weak immune system reaction, which lessens nourishment flow to support the wound healing and its repair [3].

Glycemic control has been considered as the cornerstone of the therapeutic approach in diabetes mellitus. Clinically available antidiabetic drugs have been widely used in the treatment to alleviate hyperglycemia. However, multiple risks associated with diabetes and the untoward effects of these drugs have shifted the research interest toward the use of novel plant-based antidiabetic compounds [4]. Hence, it is highly essential to find alternative drugs apart from pharmacological drugs. Zinc is the major component in maintaining the structure and function of insulin [5]. Natural products provide a tremendously promising approach to attenuate diabetes development. Thus, several plant-based compounds have provided modern medicine with herbal drugs that are currently been used in diabetic treatment. *Solenostemma argel*, known as argel, is a desert herbal plant widely grown in North African countries and traditionally used for diabetes treatment [6]. Argel may have medicinal benefits; it is traditionally being used for the management of several diseases such as pain, diabetes, respiratory tract infections, cardiovascular disorders, gastrointestinal problems, urinary tract infections, and liver and kidney diseases [7]. The leaves and/or stem of *S. argel* contain phytates and phenolics that constitute the active components that attribute to its antioxidant potency [6].

Nanotechnology is the technique used for the generation, manipulation, and usage of nanomaterials, and is developing as a talented trend in various fields for diagnostics and therapeutics processes [8]. Nanoparticles and the biological activities of metals such as silver nanoparticles (AgNPs), gold nanoparticles (AuNPs), zinc nanoparticles (ZnNPs), and zinc oxide nanoparticles (ZnONPs) can be advantageous in various capacities. Metal nanoparticles have been exploited for almost all applications in science, including but not limited to medical, physics, and geological purposes [9] as well as nonmedical purposes such as water treatment, paint, and information storage [10]. Furthermore, zinc is a major component in sustaining the assembly and role of insulin [5]. Several chemical and physical reduction methods are in use for NP synthesis [11]. The chemical production of NPs uses chemical solvents and reagents in which their end by-products may interfere with the application of the formed NPs and hence is considered as non-eco-friendly [12]. Nanodrugs contributed significantly to pre-diabetes and diabetes management [13]. Nanoparticle-based carrier systems provide a more sustained release of the bioactive agents, with an

extended duration of action apart from being target-specific [14]. Thus, canonization and nanoencapsulation provide enhanced bioavailability to the previously undeliverable drugs. Silver nanoparticles have high antifungal properties, which could be correlated to their chelating character and capability to alter the concentrations of ions present in the growth media (e.g., Ca^{2+}), essential minerals, and trace elements, which are all important for microbial growth especially for filamentous fungal growth [15]. In view of the above, diabetic wound-healing efforts have been of great concern to physicians; nonetheless, efforts were entirely unacceptable. In wound healing, nanoparticles have been ideal for topical delivery, improved cellular interactions, and are more pervasive at the wound sites. Thus, wound-healing strategies incorporating nanotherapeutics pave the way for an excellent opportunity to tackle the complexity of diabetic wound healing [16]. To the finest of our efforts, this is the first study assessing silver (Ag)/gold (Au) nanocomposites (CNPs) and nanoparticles of zinc oxide (ZnONPs) synthesized using *S. argel* extract in streptozotocin-induced diabetic rats to study various biochemical changes and evaluate the effect of the formed bioactive nanoparticles potential in the diabetic wound healing process; for which a patent has been granted by USPTO (US) [17].

2 Materials and methods

Wistar male rats were used for the present study (weighing 200–250 g). Animals were fed with typical laboratory chow food with permitted free access to water under well-ventilated conditions of 12 h day and 12 h dark cycles. The animals were allowed to acclimatize to laboratory conditions before the commencement of experiments. Protocols followed agreements and guidelines permitted by the Institutional Research Ethics Committee at King Saud University, Riyadh, Saudi Arabia. Animals were handled according to standard measures for laboratory animals used. Rats were allowed to fast 12 h before diabetes induction with streptozotocin injections ($70 \text{ mg} \cdot \text{kg}^{-1}$, i.p.). This dose of streptozotocin induces diabetes in rats. Five days later, fasting blood glucose levels were considered diabetic if higher than $150 \text{ nmol} \cdot \text{L}^{-1}$. Ten rats were allocated in each experimental group: (1) normal control group, (2) diabetic control group, (3) diabetic group that was administered metformin, (4) diabetic group treated with bulk argel, So-argel, (5) diabetic group that was administered synthesized argel Ag/Au nanoparticles, and (6) diabetic group that was administered synthesized argel zinc oxide nanoparticles.

Serum glucose was measured using commercial kits. The doses were administered orally on a daily basis to the

rats as well as by topical application on the cutaneous diabetic sores. Initially, using sanitized scissors, lesions were made while the rats were anesthetized. The lesion cuts were made with dimensions of 1 cm × 1 cm and the initial lesions were 10 ± 2 mm in the skin of rats.

2.1 Green synthesis of silver/gold nanocomposites

All reagents used were of analytical grade and were used as received and without further purification. Silver/gold nanocomposite synthesis reagents were used as received without further purification. Silver nitrate and chloroauric acid were obtained from Techno Pharmchem and Loba Chemie, India, respectively. The extract was prepared by the modified hot homogenization method [18]. *Solenostemma argel* leaves (3 g) were soaked overnight in 90 mL of boiled distilled water. Then, the extract was filtered and the filtrates were immediately used for the preparation of nanoparticles. About 1 mM silver nitrate and 1 mM chloroauric acid were individually dissolved in 50 mL of distilled water with vigorous stirring at 80°C for 5 min. Then, 5 mL of HR extract was added to the solution of both silver nitrate and chloroauric acid separately. Afterward, the colloidal solutions showed a change in color confirming the reduction of Ag^+ ions or the Au^{3+} ions, hence, indicating the formation of silver and gold nanoparticles (Figure 1). Silver nanoparticles were mixed with the solution of gold nanoparticles finalizing with an aqueous solution containing both silver and gold nanocomposite. The prepared CNPs were isolated and incubated at room temperature until further use [17].

2.2 Synthesis of zinc oxide nanoparticles

A reduced colored paste was obtained by dissolving about 0.1 M zinc acetate (Merck, 99% purity) in 50 mL of *argel* leaves extract. The extra fluid was removed, and the precipitate was washed using deionized water and ethanol three times to confirm the purity from the by-products. Finally, a colored powder was obtained by drying, which was then calcined at about 400°C [17].

2.3 Characterization of synthesized nanoparticles

Ultraviolet-visible (UV-Vis) spectral analysis was carried out using a UV 2450 Spectrophotometer (Shimadzu Corporation, Kyoto, Japan) in a range of 300–800 nm to describe the

Figure 1: Change of color in silver and gold nanoparticles.

nanocomposites. The dynamic light scattering (DLS) technique using a zetasizer (Nano series, HT Laser, ZEN3600 Malvern Instruments, Malvern, UK) was used to determine the size of the ecofriendly nanoparticles. Scanning electron microscopy (SEM) (JEOL-FE-SEM, USA) and energy dispersive spectrometry (EDS) were used for elemental analysis and confirmation of the nanoparticles' suspensions used. Elemental analysis on single particles was carried out using an Oxford Instrument, UK, Incax-act, equipped with an SEM. The size, shape, and morphology of the formed nanoparticles were determined using a transmission electron microscope (TEM) at an accelerating voltage of 100 kV; solutions were characterized on a carbon-coated copper grid. The crystalline structures of ZnONPs were scanned using X-ray powder diffraction (XRD) (Bruker D8 ADVANCE X-ray diffractometer, Bruker, Billerica, MA, USA).

3 Results and discussion

3.1 Synthesis of nanocomposites (CNPs) and UV-Vis analysis

The green synthesis of colloidal CNPs was accomplished by a wet chemical reduction of the ions (Ag^+ and AuCl_4^-) using the *S. argel* leaf extract reducing and capping agent). It is essential to ensure the dispersibility of NPs in water without a surfactant or toxic chemicals when using a noble metal NP in nanomedicine. Hence, a safe and biocompatible hydrophilic capping agent must be

used; all these requirements are fulfilled by the *S. argel* leaf extract [19]. The reddish-brown transparent colloids obtained from the initial colorless solutions indicated the synthesis of AuNPs and AgNPs. A UV-Vis spectrophotometer was used to examine the optical properties and monitor the composite nanoparticles' absorption patterns using the as-prepared argel extract (Figure 2). The AgNP solution exhibited a well-defined surface plasmon resonance band at ~ 439 nm and a small broad absorption peak, indicating the formation of rough and polydisperse AgNPs (Figure 2a). While the AuNP solution showed a very strong absorption peak and an SPR band at ~ 538.97 nm, indicating the formation of monodisperse AuNPs (Figure 2b). The spectrum of CNPs (Figure 2c) showed a slight change in the absorption bands of the prepared nanoparticles, which indicates a notably decreased absorption intensity of Ag and Au. A new wide peak at ~ 487.59 nm and a narrow peak at ~ 534.06 nm, respectively, presumably was caused by the formation of CNPs. This plausibly is explained by the possible surface restructuring process of the nanoparticles [20].

The single plasmon band splits into two peaks as specified by the theoretical spectra, one of which is located at a longer wavelength than that of silver particles, and the other is located at a slightly shorter wavelength than that of gold particles with an increasing percentage of silver [21]. Another study [22] had successfully synthesized Ag–Au alloy nanoparticles with UV-Vis absorption spectra. These spectra showed that the plasmon band remains in a single peak and shifts continuously from 400 to 520 nm with an increasing molar ratio of gold. So the Ag/Au composite particles prepared in this study are probably phase-separated composites.

3.2 DLS analysis

The DLS technique was employed to determine the hydrodynamic diameter and stability of the noble metal and

metal oxide NPs in suspension; they were determined at 25°C without any significant difference between their respective values. The results of DLS are shown in Figure 3. The hydrodynamic diameters found by DLS were 106.1 and 139.1 nm for Ag/Au and ZnONPs, respectively. The polydisperse index (PDI) of the CNP suspension was found to be 0.473, demonstrating variable sizes of the synthesized particles with very little agglomeration, which may be explained by the capping of CNPs by some biomolecules. The PDI of ZnONPs was found to be 0.269 indicating agglomeration.

3.3 TEM analysis

The TEM micrographs showed NPs to be of several sizes and dimensions, and quasi-spherical in shape with agglomeration (Figure 4). The TEM analysis for both noble metal and oxide metal NP systems is in accordance with the hydrodynamic and UV-Vis spectroscopy results.

3.4 EDS elemental analysis

Chemical compositions of CNPs and ZnONPs were determined by X-ray EDS analysis as shown in Figure 4a and b, respectively. Generally, metallic Ag and Au nanoparticles show a distinctive optical absorption peak at approximately 3 and 2.22 keV, respectively, due to their surface plasmon resonance [23,24]. The elemental profile spectrum of the synthesized nanoparticles indicated that CNPs comprise 32.34% of silver (by weight) and 28.58% of gold (by weight). Whereas, signals of others elements such as potassium and magnesium were also observed (Figure 5a). These results showed the occurrence of the plant extract (as a capping agent) on the surface of CNPs. The EDS results show that the ZnONPs synthesized according to this method resulted in 60.38% of zinc (by weight) and 39.62% of oxygen (by weight), which clearly reveals that no impurity peaks were found with the Zn and O elemental peaks (Figure 5b). The EDS spectral peak of O appears at 0.5 keV, and that of Zn appears at 1 and 8.6 keV. The EDS spectrum confirms that ZnONPs were fruitfully synthesized using a facile and quick green synthesis mode [25].

3.5 XRD analysis results

Figure 6 shows typical X-ray diffraction patterns of the synthesized ZnONPs, with bragg diffraction peaks observed

Figure 2: UV-Vis spectra of the composite nanoparticles using the argel extract.

Figure 3: Zetasizer measurement of the average size of (a) Ag/Au nanocomposite and (b) ZnONPs synthesized by the extract of HR.

at $2\theta = 31.773^\circ$, 34.441° , 36.262° , 47.559° , and 56.604° and indexed to (1 0 0), (0 0 2), (1 0 1), (1 0 2), and (2 1 0) planes of ZnO, exhibiting a crystalline wurtzite structure (JCPDS file: COD 9004178) of ZnO with little shifting. The obtained ZnONP results ensured the phase purity.

3.6 Antihyperglycemic effect

The induction of diabetes significantly ($p \leq 0.05$) increased the blood glucose levels ($310.00 \pm 10.578 \text{ mg}\cdot\text{dL}^{-1}$) compared to the control ($88.40 \pm 2.249 \text{ mg}\cdot\text{dL}^{-1}$). Treatment with bulk So-argel and its nanoformulations (CNPs and ZnONPs) significantly ($p \leq 0.05$) reduced the blood

glucose levels. The group treated with bulk So-argel ($105.00 \pm 4.041 \text{ mg}\cdot\text{dL}^{-1}$) and CNPs ($109.00 \pm 8.373 \text{ mg}\cdot\text{dL}^{-1}$) showed a more profound anti-hyperglycemic effect and were comparable to the control. The anti-hyperglycemic effect of all So-argel-treated (bulk + nanoformulations) groups was significantly ($p \leq 0.05$) more efficacious than that of the metformin-treated group (Table 1). Hyperglycemia is treated by employing many plants that are of medical importance, to regulate diabetes, which improve glucose consumption by body cells or by decreasing carbohydrates absorption by inhibition of α -amylase activity and decreasing gluconeogenesis. The investigation in this study suggested that bulk argel had the ability to moderate sugar levels due to diabetes. This could be attributed to the

Figure 4: TEM micrographs of (a) the nanocomposite and (b) zinc oxide nanoparticles synthesized using the extract of HR.

Figure 5: EDS spectra of (a) Ag/AuNPs and (b) ZnONPs synthesized using the So-argel leaf extract.

Figure 6: XRD patterns of the synthesized calcined ZnONPs.

presence of biochemical ingredients such as pyrene glycosides, flavonoids, kaempferol, quercetin, rutin, flavonols, flavanones, chalcones, and alkaloids that are present in the argel [26]. Argel is recommended to be used to cure different diseases (kidney disease, liver, respiratory system). Leaves of argel can be also used as anti-inflammatory, antiseptic,

vasodilatory, and hypotensive agents [27]. Furthermore, nanoparticles allow the controlled release of the drug into intra-tissues without invasive approaches. As the retention time is enhanced, the quantity of medication being absorbed also increases as well as its bioavailability, thereby minimizing the risk of adverse side effects.

To avoid hyperglycemia or lessen the signs, preventive strategies through nonpharmacological methods can be followed. A healthy diet, workout, and weight control can regulate serum glucose and alleviate regular glucose uptake. When lifestyle change fails to treat diabetes, medicines become a requirement. In type I diabetes, therapeutic insulin replacement is introduced. On the contrary, medications were designed to mark type II diabetes, with different styles of action. Nowadays, several drugs are commercially available but are limited by their pharmacokinetic properties, action, as well as side effects [4]; hence, using herbal medicines becomes important. Indeed, both herbal/synthetic medicines have to follow a comprehensive scientific inspection via screening,

Table 1: Blood glucose levels (mean $\pm$ SE) of rats in the experimental groups

Experimental groups	Mean blood glucose level (mg·dL ⁻¹)
Control	88.40 $\pm$ 2.249 ^a
Diabetic control	310.00 $\pm$ 10.578 ^b
Metformin-treated	134.00 $\pm$ 0.927 ^c
Argel bulk (So-argel)	105.00 $\pm$ 4.041 ^a
So-argel Ag–Au nanoparticles (CNPs)	109.00 $\pm$ 8.373 ^a
So-argel ZnO nanoparticles (ZnONPs)	118.00 $\pm$ 1.452 ^d

Different letters indicate a significant difference ($p \leq 0.05$).

validation, preclinical. and clinical trials for the assessment of their efficacy and toxic levels [28].

3.7 Liver and kidney tests

The diabetic control group showed significantly ($p \leq 0.05$) enhanced levels of serum AST (464.80 $\pm$ 3.006 U·L⁻¹) and ALT (457.60 $\pm$ 16.424 U·L⁻¹) in comparison to those of the control group (AST: 271.80 $\pm$ 9.759 and ALT: 68.60 $\pm$ 2.874 U·L⁻¹), respectively. Treatment with bulk So-argel (170.33 $\pm$ 20.431 U·L⁻¹) and CNPs (228.33 $\pm$ 11.464 U·L⁻¹) significantly ($p \leq 0.05$) decreased the AST levels in diabetic rats' serum. However, treatment with So-argel ZnO was not significantly effective. Serum ALT levels in diabetic rats were also significantly ($p \leq 0.05$) reduced on treatment with bulk So-argel (38.00 $\pm$ 3.05 U·L⁻¹) as well as with both the nanoformulations, CNPs (48.00 $\pm$ 5.291 U·L⁻¹) and ZnONPs (63.66 $\pm$ 6.887 U·L⁻¹). Hence, the overall liver function tests were significantly ($p \leq 0.05$) improved with the So-argel treatments as compared to the group treated

with metformin (Table 2). The liver plays a vital role in glucose metabolism and the detoxification of free radicals [29]. Liver damage is associated with elevated transaminases like AST and ALT [30]. A damaging liver may result in leakage of AST, ALT, and ALP enzymes from its cytosol into the bloodstream, hence, elevating these enzymes levels [31]. While some changes were not substantial, it is suggested to increase the test period to investigate the liver enzyme levels changes more accurately. Curcumin-ZnO (10 mg·kg⁻¹, 21 days) nanoparticles were claimed to be more effective than curcumin nanoparticles (50 mg·kg⁻¹, 21 days) in diabetes therapy in terms of reduction of blood glucose, improvement in serum insulin, and activation of glucose transporter 2 (GLUT 2) and glucokinase genes in pancreas and liver (type 2 diabetic rats) [32]. Diabetes also causes kidney dysfunction and increased serum levels of uric acid, urea, and creatinine [33]. Blood urea levels were significantly ($p \leq 0.05$) elevated in the diabetic control group (81.80 $\pm$ 1.280 mg·dL⁻¹) in comparison to the control group (42.40 $\pm$ 1.568 mg·dL⁻¹). Similarly, significantly enhanced levels of serum creatinine were also observed in the diabetic control group (0.58 $\pm$ 0.019 mg·dL⁻¹) when compared with those in the control group (0.37 $\pm$ 0.020 mg·dL⁻¹). This suggested that renal dysfunction and possible kidney injury occurred in control diabetic rats due to severe hyperglycemia [33]. Serum urea and creatinine are useful indices for evaluating the status of renal function. An increase in the level of serum urea may imply impaired renal excretion [34]. Treatment with bulk So-argel and its nanoformulations, CNPs and ZnONPs, significantly ($p \leq 0.05$) reduced blood urea and serum creatinine levels among diabetic rats. Nonetheless, treatments between blood urea levels were not significantly different. Nevertheless, the effects of bulk So-argel and CNPs on serum creatinine levels were significantly more pronounced than the effect of ZnONPs. The groups treated with both bulk So-argel and

Table 2: Liver and kidney functions tests (mean $\pm$ SE) of rats in the experimental groups

Experimental groups	Serum AST levels (U·L ⁻¹)	Serum ALT levels (U·L ⁻¹)	Blood urea levels (mg·dL ⁻¹)	Serum creatinine levels (mg·dL ⁻¹)
Control	271.80 $\pm$ 9.759 ^a	68.60 $\pm$ 2.874 ^a	42.40 $\pm$ 1.568 ^a	0.37 $\pm$ 0.020 ^a
Diabetic control	464.80 $\pm$ 3.006 ^b	457.60 $\pm$ 16.424 ^b	81.80 $\pm$ 1.280 ^b	0.58 $\pm$ 0.019 ^b
Metformin-treated	421.80 $\pm$ 1.319 ^b	112.60 $\pm$ 1.249 ^c	77.80 $\pm$ 1.019 ^b	0.54 $\pm$ 0.007 ^b
Argel bulk (So-argel)	170.33 $\pm$ 20.431 ^a	38.00 $\pm$ 3.05 ^a	36.33 $\pm$ 0.881 ^a	0.26 $\pm$ 0.007 ^c
So-argel Ag–Au nanoparticles (CNPs)	228.33 $\pm$ 11.464 ^a	48.00 $\pm$ 5.291 ^a	35.00 $\pm$ 0.577 ^a	0.24 $\pm$ 0.018 ^c
So-argel ZnO nanoparticles (ZnONPs)	403.66 $\pm$ 75.180 ^b	63.66 $\pm$ 6.887 ^a	47.00 $\pm$ 7.505 ^a	0.41 $\pm$ 0.289 ^a

Different letters indicate a significant difference ($p \leq 0.05$).

its nanoformulations showed a significantly ($p \leq 0.05$) thoughtful result on the kidney functions of diabetic rats in contrast to the group treated with metformin, the commercial drug (Table 2).

Plant extracts usually control high blood glucose levels by the stimulation of pancreatic secretion of insulin from β -cells in Langerhans islets and amplified glucose transportation in the blood to peripheral tissues [35]. Bulk argel extracts and their nanoconjugates might have direct effects on the residual beta cell secretion and probably increase glucose peripheral utilization; furthermore, the small size of NPs causes both greater mobility as well as potentially enhanced uptake across biological membranes.

3.8 Lesions

Figures 7 and 8 illustrate a marked enhancement in the size of the lesion among the rats treated with synthesized argel extract with silver/gold nanocomposite particles in comparison to the groups treated with metformin and ZnONPs, indicating a more profound effect of CNPs on the diabetic wound healing (Figure 8). The wound-healing efficacy of ZnONPs was also comparable to that of metformin. Thus, both the nanoparticles with the argel extract showed a potent therapeutic effect on wound healing. The key factor incriminated in the enhanced illness and death due to diabetes is associated with vascular complications as well as the failure of the wound remediation processes in diabetics [36]. Diabetic lesions are associated with reduced wound healing due to unsuitable cellular and cytokines response, infection, poor vascularization, and neuropathy [37].

Beneficial therapeutic approaches for the management of diabetic wounds could be achieved through a

Figure 7: Wound closure rate (lesion area in mm²) in animals after lesioning and treatment with metformin (MT), gold–silver nanocomposite (CNPs), and zinc oxide nanoparticles (ZnONPs).

Figure 8: Images of wound closure in animals after lesioning (DC) and treatment with metformin (MT), gold–silver nanocomposite (CNPs), and zinc oxide nanoparticles (ZnONPs) at the end of the experimental period.

deeper understanding of the molecular mechanism and pathophysiology of wound healing. Extracts of medicinal plants have been documented to arrest bleeding from fresh wounds, inhibit microbial growth, and promote wound healing [38]. The effects of medicinal plants on wound healing may be attributed to the free radical scavenging action of phytochemicals in the extracts acting either singly or synergistically. The active compounds improve wound healing by increasing the ability and strength of collagen fibrils; moreover, they enhance blood circulation and avoid cell damage [36]. In recent years, nanoparticles such as silver, gold, and zinc having antibacterial and antibiotic properties along with low *in vivo* toxicity contributed an incomparable approach to quickening the wound healing of both delayed acute and chronic wounds [39]. In line with the study, it has been shown that gold nanoparticles have been of great interest because of their biocompatibility, noncytotoxicity, and other attractive properties such as surface modification [40]. Also, the lowest bactericidal properties of NPs are observed with ZnONPs using different volumes of the zinc salt with clove extract [41]. Similarly, the synthesized AgNPs showed successful antibacterial activity against bacteria [42]. Nanoparticles incorporated with biopolymers or biomaterials act as potential wound-healing material in the treatment of diabetic wounds. Accordingly, the present study showed deep wound healing using nanoparticles along with the plant material, *S. argel* leaf extract. It is

expected that the nanocomposites can be used as a cream or in the form of drops for topical application on the diabetic wound.

4 Conclusion

The results of the current study conclude that *S.argel* has a potent antidiabetic effect, which was further enhanced with the nanoformulations incorporating noble metals/metal oxide (Au/Ag, ZnO), both been documented to have their own therapeutic efficacy. Further, all treatments with *S. argel* showed a more profound antidiabetic effect in comparison to the synthetic drug used. Thus, such nano-therapeutic strategies that are safe and cost-effective offer novel approaches, which will fully exploit the advancement of nanotechnology to combat the increasing prevalence of Type-2 diabetes in the near future.

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