

RESEARCH ARTICLE

Formulation, characterization, and in vivo evaluation of a nanoengineered herbal gel containing *Rhododendron arboreum* and *Quercus leucotrichophora* for chronic wound healing

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ABSTRACT

Chronic wounds remain a major clinical challenge due to prolonged inflammation, microbial infection, impaired angiogenesis, and delayed tissue regeneration. In this study, a nanoengineered herbal gel containing *Rhododendron arboreum* and *Quercus leucotrichophora* extracts for enhanced chronic wound healing. Hydroalcoholic extracts of both plants were prepared by Soxhlet extraction and employed in the green synthesis of silver nanoparticles, which were subsequently incorporated into a Carbopol 940-based nanogel. The resulting formulation was characterized using Fourier-transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). In addition, Physicochemical properties, including pH, viscosity, Spreadability, homogeneity, and drug content, were also evaluated. FTIR analysis indicated good compatibility between the herbal extracts, nanoparticles, and excipients, while SEM and TEM micrographs confirmed the homogeneous distribution of nanoparticles throughout the gel matrix. The wound-healing efficacy was further examined using an excision wound model in Albino Wistar rats, where the optimized nanogel produced significantly enhanced wound contraction, accelerated epithelialization, increased collagen deposition, and improved tissue regeneration relative to the disease control group. By the sixteenth day, the high-dose treatment group achieved approximately 96% wound contraction, closely matching the standard treatment group (~96-98%). Overall, these results demonstrated that the developed nanoengineered herbal gel has considerable potential as effective phytopharmaceutical platform for chronic wound management and future advanced topical wound-care applications.

Keywords: Herbal nanogel; wound healing; silver nanoparticles; nanoengineered formulation; nanomedicine

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1. Introduction

The skin is the largest and one of the most important organs of the human body and serving as the primary protective barrier microbial invasion, physical injury, and environmental stressors while maintaining tissue homeostasis (Walker, 2022). When skin integrity is compromised, a complex wound-healing process is initiated involving haemostasis, inflammation, proliferation, and tissue remodelling. Acute wounds normally heal in a predictable period of time. However, chronic wounds, including diabetic foot ulcers, venous leg ulcers, and pressure ulcers, often do not proceed through the normal stages of healing, resulting in prolonged inflammation, persistent infection, impaired angiogenesis, and delayed tissue regeneration (Almadani et al., 2021; Kangal and Kopitnik, 2025). Chronic wounds are a major global healthcare burden negatively affecting patient quality of life while increasing morbidity and healthcare expenditure (Maheshwari, 2024; Darwin and Tomic-Canic, 2018). Conventional wound-care methods strategies, such as topical

antimicrobial agents, antiseptics, and synthetic dressings are widely used to treat wound infection and promote healing. However, these approaches are often accompanied by limitations such as poor tissue penetration, inadequate retention at the wound site, frequent administration and the emergence of antimicrobial resistance (Tan et al., 2023). These challenges have stimulated interest in the development of advanced drug-delivery systems capable of enhancing local therapeutic efficacy while simultaneously supporting tissue regeneration (Saghazadeh et al., 2018). Medicinal plants have been used in healthcare for quite some time as potent agents for treating physical injuries and skin diseases (Rubiya et al., 2025). Plant-derived secondary metabolites such as flavonoids, phenolic compounds, tannins, terpenoids, and alkaloids have possessed antioxidant, antimicrobial, anti-inflammatory, and collagen-stimulating properties that collectively contribute to different stages of the wound-healing process (Bhatt et al., 2022). *R. arboreum* (Buransh) is one of the medicinal plants rich in flavonoids and phenolic compounds with demonstrated antioxidant and

anti-inflammatory properties (Jha et al., 2024). Similarly, *Q. leucotrichophora* (Banjoak) contains tannins and polyphenolic compounds known for their antimicrobial, astringent and tissue repairing activities (Taib et al., 2020; Burlacu et al., 2020). The complementary pharmacological profiles of these plants suggest the potential for their synergistic use in wound management. Wound healing is a complex cascade of biological events. Recent advances in nanotechnology have provided new approaches for wound treatment. Delivery systems based on nanoparticles improve the stability, bioavailability, tissue penetration and controlled release of bioactive compounds (Mamun et al., 2024; Hajialyani et al., 2018; Eskandar, 2025). Silver nanoparticles have attracted considerable attention due to their broad-spectrum antimicrobial activity, ability to reduce microbial colonization and potential to accelerate tissue repair (Khalifa et al., 2025; Rybka et al., 2022). In addition, nanogel-based formulations offer the advantages of nanoparticles along with the good rheological properties of hydrogels, leading to increased residence time at the wound site, better drug permeation and prolonged therapeutic efficacy (Delgado-Pujol et al., 2025; Kianfar et al., 2025). Although various herbal nanogel systems have been investigated for wound healing, investigations on combined therapeutic potential of *R. arboreum* and *Q. leucotrichophora* in a nanoengineered delivery platform are scarce. Therefore, the present study was designed to develop a Carbopol based nanoengineered herbal gel incorporated with green synthesized silver nanoparticles using hydroalcoholic extracts of *R. arboreum* and *Q. leucotrichophora*. The formulation was characterized using physicochemical and nanotechnological techniques followed by evaluation of its wound-healing efficacy in an excision wound model using Albino Wistar rats. This study aims to provide experimental evidence supporting the development of a novel phytopharmaceutical nanogel for advanced chronic wound management.

2. Materials and methods

2.1 Materials

Fresh plant samples of *R. arboreum* and *Q. leucotrichophora* were harvested from the Himalayan region of Uttarakhand, India. The collected plant material leaves were thoroughly rinsed with distilled water to remove adhering dust and other impurities before further processing. Standard commercial vendors provided the hydroalcoholic solvent (Ethanol: water), Carbopol 940, triethanolamine, methyl paraben, silver nitrate, distilled water, and other analytical-grade chemicals and reagents that were utilized without additional purification.

2.2 Preparation of Hydroalcoholic Herbal extract

Plant materials of *R. arboreum* and *Q. leucotrichophora* were authenticated by a qualified taxonomist, thoroughly washed, shade dried under ambient conditions, and subsequently pulverized into a coarse powder. Voucher

specimens are deposited in the departmental herbarium for future reference. The defatted residue was extracted with a hydroalcoholic solvent system (ethanol, 60:40 v/v) at 70°C for 16 h, as previously described (Harborne, 1998). The extraction process was continued until all plant material was processed. The resulting extracts were filtered through Whatman No. 1 filter paper and concentrated under reduced pressure in a rotary vacuum evaporator maintained below 45°C to obtain semisolid crude extracts. The concentrated extracts were re-dissolved in 50% ethanol and stored at 4°C until use. For preparation of herbal composition for synthesis of nanoparticles and nanogel formulation, equal proportions (1:1, 50:50) of extract of both plants were combined.

2.3 Synthesis of nanoparticles

The biosynthesis of silver nanoparticles (AgNPs) was carried out by using an equal mixture of hydroalcoholic extracts of *R. arboreum* and *Q. leucotrichophora* as reducing and stabilizing agent following a green synthesis approach reported previously (Vanlalveni et al., 2021; Asif et al., 2022). The herbal extract was mixed with aqueous solution of silver nitrate under constant magnetic stirring at room temperature. The reaction mixture changed colour from pale yellow to dark brown. This was a gradual process and showed the formation of silver nanoparticles by surface plasmon resonance (Vanlalveni et al., 2021). The synthesized nanoparticles were harvested by centrifugation and washed several times with distilled water to remove unreacted constituents and dried for further characterization and utilization in the nanogel formulation. The phytoconstituents were incorporated with silver nanoparticles to improve the antimicrobial activity, bioavailability and wound-site retention.

2.4 Preparation of herbal nanoengineered gel

Carbopol 940 served as the polymeric gelling agent for preparing the nanoengineered herbal gel. In short, a uniform dispersion was achieved by homogenizing 0.7% (w/v) Carbopol 940 in distilled water at a speed of 50-60 rpm. Under constant stirring, 0.1% triethanolamine and 0.1% methyl paraben were added to this dispersion. The gel basis was mixed with a previously prepared herbal composition that contained equal amounts of extracts from *Q. leucotrichophora* and *R. arboreum*. After that, the green-synthesized silver nanoparticles were incorporated into the gel matrix. To create a consistent nanoengineered herbal gel, the mixture was completely homogenized. For further analysis, the prepared gel was kept at room temperature in airtight containers.

2.5 Characterization of Nanoformulations

2.5.1 FTIR analysis

FTIR spectra of crude extract, silver nanoparticles and herbal nanogel were recorded from 4000-400 cm⁻¹ for

identification of functional groups and possible interaction between phytoconstituents and nanoparticles.

2.5.2 SEM analysis

The surface morphology and microstructure of the nano-engineered gel were analyzed by means of SEM to evaluate the structural organization and porosity of the gel formulation.

2.5.3 TEM analysis

Transmission Electron Microscope (TEM) analysis was conducted in order to find the morphology, particle size, and distribution of silver nanoparticles present in the gel matrix.

2.6 Physicochemical evaluation

Spreadability was determined by slip and drag method. Viscosity was measured by Brookfield viscometer and pH was measured by calibrated digital pH meter. The drug content uniformity was determined spectrophotometrically after suitable dilution of the formulation (Fox, 2006).

2.7 Experimental animals

The experiment used healthy adult male albino rats of Wistar strain and weighing from 150 to 200 grams each. These animals were procured from the animal house of the Department of Pharmaceutical Sciences of Gurukula Kangri (Deemed to be University), Haridwar, Uttarakhand, India. They were kept under controlled laboratory conditions where temperature was around $25 \pm 2^\circ\text{C}$, relative humidity was between 30-70% with a 12-hour dark/light cycle and free access to standard pellet food and water.

2.8 Excision wound model

The wound-healing study was performed using the excision wound model described by Morton and Malone, 1972. The percentage of wound contraction was calculated according to the following equation:

$$\% \text{ Wound Contraction} = \left[\frac{\text{Initial Wound Area} - \text{Wound Area on Specific Day}}{\text{Initial Wound Area}} \right] \times 100$$

The period of epithelialization was recorded as the number of days required for complete wound closure characterized by the formation of new epithelial tissue without any exposed wound surface. The animals were randomly divided into five different groups (each containing six animals). Group I was used as the normal control, Group II was used as the disease control, Group III and Group IV were administered low- and high-doses of the Nano formulations, respectively, and Group V was administered the standard treatment (Soframycin® cream).

Group I: Normal Control

- Group II: Disease Control

- Group III: Treatment Group I (Low-dose nano formulation)
- Group IV: Treatment Group II (High-dose nano formulation)
- Group V: Standard Treatment (Soframycin® cream)

The animals were anesthetized by intraperitoneal injection with ketamine hydrochloride (25 mg/kg) and xylazine hydrochloride (10 mg/kg). The full-thickness wounds with 8 mm diameter were made in the dorsum after shaving with a sterile biopsy punch. The topical therapy was administered twice a day for 16 days and the wound size was measured on days 3, 7, 10, 13, and 16.

2.9 Statistical analysis

The experimental data were shown as mean $\pm$ standard deviation (SD). The statistical analysis was done using ANOVA, and Tukey's multiple comparison test was used for analysing the differences between the groups. Statistically significant values were defined as $p < 0.05$.

3. Results and discussion

3.1 Phytochemical screening

The preliminary phytochemical screening of hydroalcoholic extracts of *R. arboreum* and *Q. leucotrichophora* showed the presence of several important bioactive phytoconstituents like phenols, flavonoids, proteins, steroids and tannins. Alkaloids, saponins and quinones were not detected and summarized in **Table 1**. These phytoconstituents play a significant role in different stages of wound healing because of their antioxidant, antimicrobial, anti-inflammatory and collagen promoting properties. Free radical scavenging activity may be due to the presence of flavonoids and phenolic compounds. Wound contraction and tissue repair are due to the presence of tannins. Collectively, these findings establish a phytochemical basis for the observed wound-healing activity and support the utilization of these herbal extracts in the development of an effective nanoengineered wound-healing formulation.

Table 1. The results of preliminary phytochemical screening showing the presence of bioactive compounds in the hydro-alcoholic herbal extracts.

S. No.	Phytoconstituent	Test Performed	Observation	Result
1	Alkaloids	Dragendorff's Test	No reddish-brown precipitate observed	-
2	Phenols	Ferric Chloride Test	Green coloration observed	+
3	Flavonoids	Shinoda Test	Pink to crimson coloration observed	+
4	Saponins	Foam Test	No persistent foam observed	-
5	Proteins	Biuret Test	Violet coloration observed	+
6	Quinones	Concentrated H_2SO_4 Test	No characteristic red coloration observed	-
7	Steroids	Salkowski Test	Reddish-brown ring formed at the interface	+

8	Tannins	Ferric Chloride Test	Bluish-black coloration observed	+
Present (+), Absent (-)				

3.2 FTIR spectra

FTIR spectroscopy was performed to investigate the chemical compatibility among the herbal extract, silver nanoparticles, and the Carbopol-based gel matrix. FTIR spectrum exhibited characteristic absorption peaks at ~3380 cm⁻¹ due to O-H stretching vibrations of phenolic compounds, 2925cm⁻¹ due to aliphatic C-H stretching, 1630 cm⁻¹ due to carbonyl (C=O) stretching vibrations associated with flavonoids and phenolic constituents, and 1100 cm⁻¹ due to C-O stretching vibrations of polyphenolic compounds. Additional minor peaks in the region 1380-1400 cm⁻¹ might be due to C-N stretching vibrations of proteinaceous compounds. No significant peak shifting, no disappearance or formation of new peaks was observed after incorporation into the gel matrix which indicates no chemical incompatibility between the phytoconstituents, nanoparticles and formulation excipients. These findings confirm the successful encapsulation of herbal constituents within the nanoengineered gel system (Fig. 1).

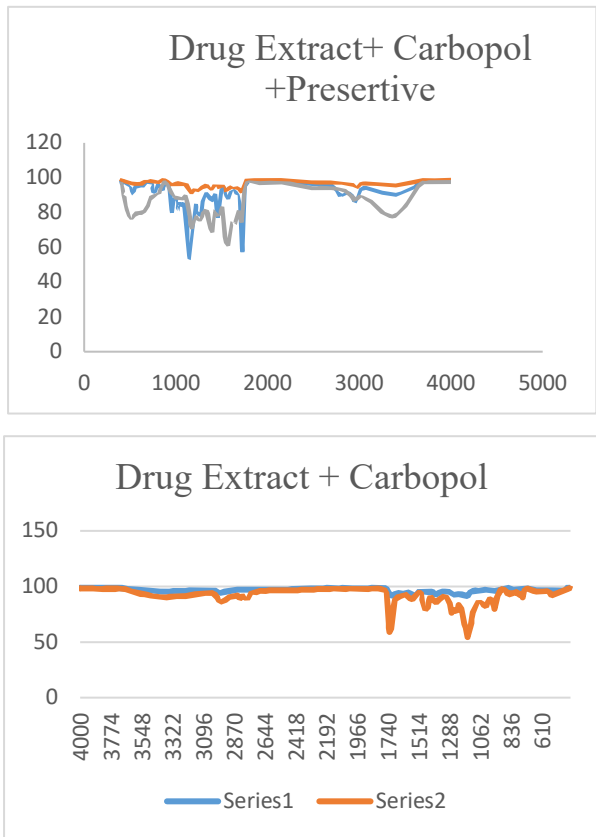


Fig. 1. FTIR spectra of herbal extract, Carbopol, and optimized nanoengineered gel formulation.

3.3 SEM and TEM imaging

SEM micrographs revealed a highly porous and interconnected surface morphology with pore size ranging from approximately 4.2–701.2 μm , facilitating

moisture retention and sustained release of phytoconstituents (Fig. 2). Such Porous architecture may improve hydration, oxygen diffusion, bio adhesion, and sustained release of bioactive constituents. The TEM analysis showed that the spherical nanoparticles were uniformly distributed within the gel matrix with very low aggregation, which suggested the successful development of the Nanoformulations and good colloidal stability (Fig. 3). The distribution observed at nanoscale supports improved penetration and retention of phytoconstituents at the site of wound.

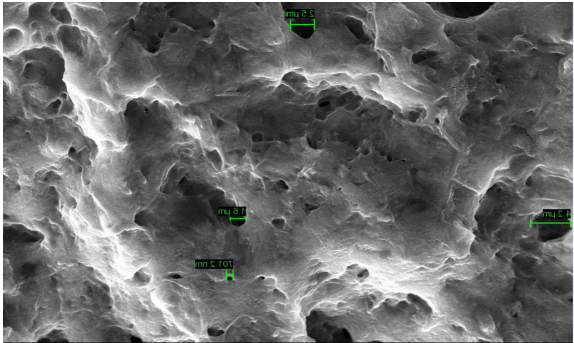


Fig. 2. SEM micrographs showing porous nanogel surface morphology.

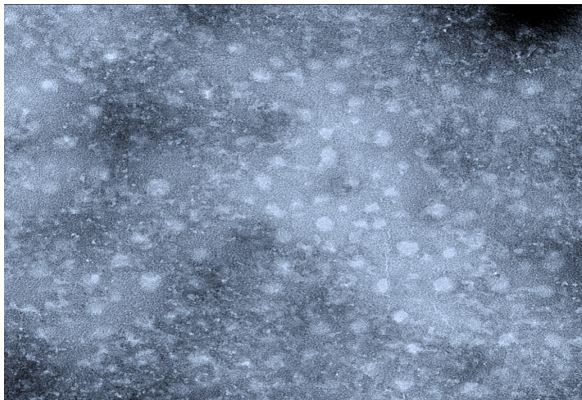


Fig. 3. TEM images demonstrating spherical nanosized particles uniformly distributed within the gel matrix.

3.4 Physicochemical evaluation

The optimized nanogel exhibited desirable physicochemical characteristics for topical application, which are presented in **Table 2**. The formulation maintained a pH of 6.45 ± 0.12 , which is compatible with normal skin physiology and minimizes the likelihood of irritation. Good Spreadability ($15.2 \pm 0.6 \text{ g}\cdot\text{cm/s}$) and appropriate viscosity ($4620 \pm 110 \text{ cP}$) ensured easy application and prolonged residence at the wound surface. Furthermore, the formulation demonstrated excellent homogeneity and high drug content uniformity ($97.8 \pm 1.4\%$), confirming consistency and stability. These properties collectively indicate that the nanogel is suitable for long-term wound-healing applications.

Table 2. Physicochemical evaluation of optimized nanogel.

Parameter	Observation
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Appearance	Homogeneous gel
Color	Brownish green
pH	6.45±0.12
Spreadability	15.2±0.6 g·cm/s
Viscosity	4620±110 cP
Homogeneity	Excellent
Drug Content	97.8±1.4 %

The produced nanogel formulation's stability and suitability for long-term wound treatment were validated by the physicochemical properties.

3.5 Wound healing activity

Representative wound photographs taken during the study period (days 0, 3, 7, 10, 13 and 16 confirmed progressive wound closure in Treatment Groups I and II as comparable to the disease-control group. Both treatment groups displayed a higher speed of wound closure in all experimental days, with the high dose formula (Treatment Group II) having almost healed wounds by day 16. The qualitative observations were consistent with the quantitative observations regarding wound contraction which were given in Table 3 and Figs. 4 & 5. The herbal nanoengineered gel exhibited significant wound healing effect. As shown in Table 3, On the 3rd day, Treatment Groups I and II showed 11% and 12% wound contraction, respectively, compared with 5% in the disease control group and 16% in the standard group. Both groups I and II showed 39% and 40% percentage wound contraction whereas the disease-control group showed only 21% contraction and standard group showed 44% contraction on the 7th day. Wound contraction increased to 55% and 56% in Treatment Groups I and II by the 10th day as compared to 29% in the disease control group and 60% in standard group. On the 13th day, the treatment with groups exhibited 74% and 76% wound contraction, while disease control and standard groups showed 38% and 80% contraction, respectively. The graphical representation of wound contraction clearly demonstrated superior healing performance of the nanoengineered herbal gel compared with the disease control group. On the other hand, improvement was observed on the 16th day, treatment with groups I and II achieved 94% and 96% wound contraction, respectively, which was comparable to the standard group (98%) and substantially higher than the disease-control group (50%). Previous studies have reported that *Aloe vera* hydrogel formulations have been reported to achieve about 92% wound contraction by day 14 and complete wound closure by day 21, mainly through the stimulation of fibroblast proliferation, collagen deposition and epithelial regeneration (Meza-Valle et al., 2021). Formulations of *Centella asiatica* have also exhibited increased wound contraction and complete or near complete wound healing within 12-14 days by promoting angiogenesis, collagen synthesis, fibroblast proliferation and extracellular matrix

remodelling (Somboonwong et al., 2012). Plant-mediated silver nanoparticles based wound dressings have demonstrated fast wound closure (Chinnasmay et al., 2021; Gusmão et al., 2024).

Table 3. Effect of herbal nanoengineered gel on percentage wound contraction in excision wound model.

Day of Observation	Disease Control	Treatment Group I	Treatment Group II	Standard Group
3 rd Day	5%	11%	12%	16%
7 th Day	21%	39%	40%	44%
10 th Day	29%	55%	56%	60%
13 th Day	38%	74%	76%	80%
16 th Day	50%	94%	96%	98%

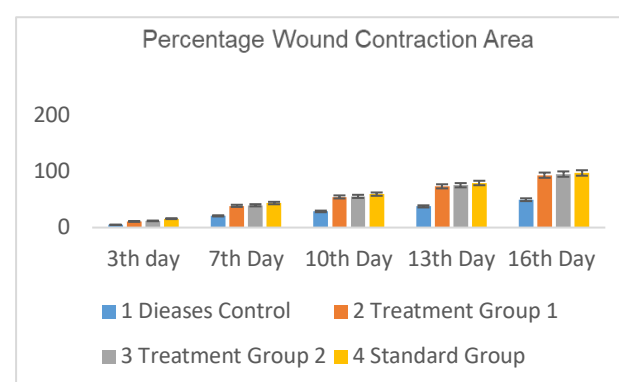


Fig. 4. Comparative percentage wound contraction profile of disease control, treatment groups, and standard treatment group over the 16-day study period.

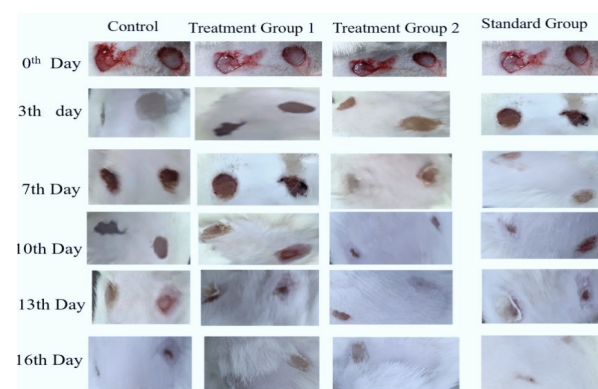


Fig. 5. Representative wound photographs showing progressive wound contraction in different treatment groups during the 16-day study period.

3.6 Histopathological evaluation

Histopathological examination of wound tissues revealed enhanced tissue regeneration in the treatment groups compared with the disease control group. As shown in Fig. 6, the treated groups exhibited increased collagen deposition, fibroblast proliferation,

angiogenesis, and epithelialization, as well as reduced inflammatory cell infiltration compared with disease control. The presence of a continuous epithelial lining along with the organized collagen fiber formation indicates increased efficiency of the wound healing process. The findings from these microscopic observations support the data from the wound contraction experiment and confirm the effectiveness of the herbal-based engineered gel in the tissue regeneration process.

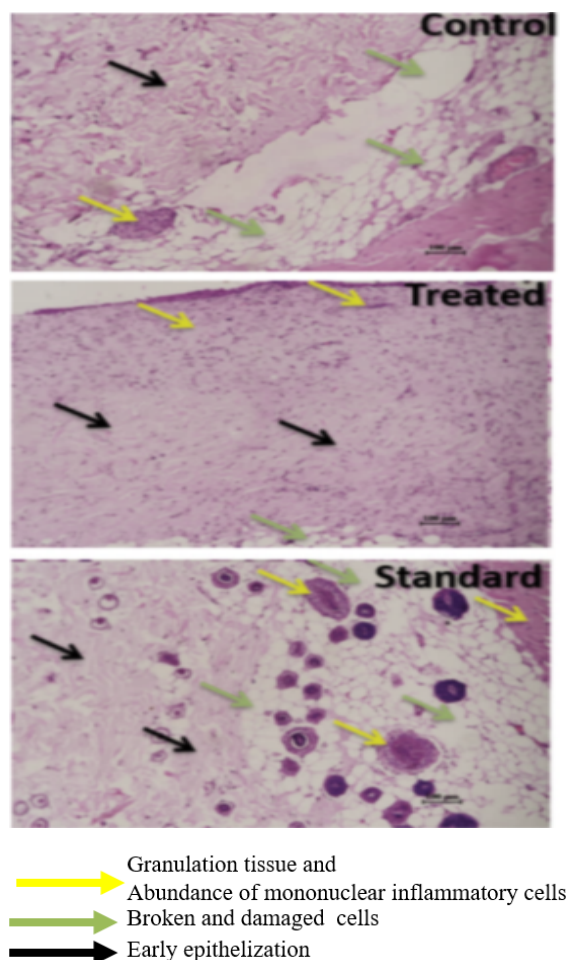


Fig. 6. Representative H&E-stained sections showing enhanced collagen deposition, fibroblast proliferation, epithelial regeneration, and reduced inflammatory infiltration in treated groups compared with disease control.

3.7 Mechanistic insights and therapeutic significance

To enhanced wound-healing response observed in this study is likely attributable to the combined therapeutic effects of the phytoconstituents and the nanotechnology-based delivery system. SEM analysis demonstrated a porous and interconnected gel architecture, while TEM revealed a homogeneous distribution of silver nanoparticles throughout the gel matrix. Similar nanogel systems have been reported to improve tissue penetration, bioavailability and wound healing efficacy via controlled drug release and enhanced cellular interactions (Hajjalyani et al., 2018; Delgado-Pujol et al., 2025; Kianfar et al., 2025). Studies on *Aloe vera*

hydrogels and *Centella asiatica* formulations have also demonstrated accelerated collagen synthesis, angiogenesis, and epithelial regeneration, supporting the role of plant-derived biomolecules in wound repair (Preethi et al., 2009). Furthermore, silver nanoparticles are also involved in antimicrobial activity and prevention of microbial colonization, thereby promoting tissue regeneration and wound repair (Khalifa et al., 2025; Rybka et al., 2015). The high dose formulation showed 96% wound contraction indicating that the nanoengineered herbal gel is comparable to other advanced nanotechnology assisted wound healing systems reported in the literature (Moeini et al., 2020; Boateng et al., 2015).

4. Conclusions

In this investigation study, successfully developed and experimentally evaluated a nanoengineered herbal gel containing *R. arboreum* and *Q. leucotrichophora* extracts for chronic wound-healing applications. The optimized formulation demonstrated favourable physicochemical characteristics, including appropriate pH, viscosity, Spreadability, high drug content uniformity, and excellent colloidal stability. Nanotechnological characterization confirmed the successful formation of uniformly distributed silver nanoparticles with nanoscale dimensions, supporting enhanced delivery of bioactive phytoconstituents. In the excision wound model, the formulation exhibited significant wound-healing activity as indicated by increased wound contraction, collagen deposition, epithelialization, angiogenesis and decreased inflammatory response as compared to disease control group. The synergistic effects of the phytochemical constituents and silver nanoparticles contributed to improved tissue regeneration and faster wound repair. Overall, the developed nanoengineered herbal gel represents a promising phytopharmaceutical approach for chronic wound management and may serve as an effective alternative to conventional topical therapies. Further studies involving long-term stability assessment, mechanistic investigations, and clinical evaluation are warranted to establish its therapeutic potential for human wound-care applications.

Credit authorship contribution statement

RS, TK, RB: Conducting Experiments/Data collection, Conceptualization, Methodology, Investigation, Writing – Original Draft.

S.K.R, G.G: Methodology, Validation, Data Curation, Review & Editing,

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None.

Conflict of interest

The authors declare no conflict of interest.

Data availability

The author can provide data supporting the inquiry findings upon reasonable request.

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