

Original Article

PREPARATION AND CHARACTERIZATION OF FICUS LACOR METALLIC PARTICLES BASED NANOGEL FOR WOUND HEALING ACTIVITY

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ABSTRACT

Objective: Since there is no evidence of silver nanoparticle preparation using the *Ficus lacor* plant, our present study was designed to synthesise silver nanoparticles using a *Ficus lacor* leaves extract, which was expected to show an enhanced wound healing activity with greater advantages of green synthesis.

Methods: In the present study, silver nanoparticles were prepared using *Ficus lacor* leaf extract and the prepared nanoparticles were characterised by Ultraviolet-Visible spectroscopy and Particle size analysis later a topical gel is prepared and its effectiveness was evaluated by using animal excision wound model.

Results: The study results showed that the *Ficus lacor*-based silver nanoparticle topical gel on an animal excision wound model exhibited almost similar wound healing activity in comparison with standard marketed product.

Conclusion: This study concluded that *Ficus lacor*-silver nanoparticle gel showed considerable improvement in the excision wound model and hence this can be a promising candidate in wound healing.

Keywords: Wound healing, Nanotechnology, Silver nanoparticles, Green synthesis, *Ficus lacor*

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INTRODUCTION

A wound is described as a detriment or destruction to the typical anatomy and physiology. Wounding, regardless of the cause or nature, injures the tissue as well as interrupts the nearby surrounding within it. Normal wound healing takes place in a dynamic and intricate way encompassing a sequence of coordinated events such as hemostasis, inflammation, proliferation and tissue remodelling stages [1]. When normal wound healing fails as in persistent injuries that don't heal and would be extremely expensive and reduced quality of life in the society [2]. As per a 2018 retrospective analysis study of Medicare enrollees revealed that 8.2 million people had wounds with or without infections. The estimated costs to Medicare for both acute and chronic wound therapy were between \$28.1 billion and \$96.8 billion [3]. Looking into the therapy, wound healing treatment has gone through a great revolution. The various methods are used in treating wounds, such as debridement, skin substitutes, growth factors, wound dressings, gene therapy, stem cell therapy, antiseptics, antibacterial agents [4], traditional therapy-based herbal and animal-derived compounds, living organisms [5].

Another treatment option that is grabbing greater attention is nanotechnology. The study of incredibly small structures is known as nanotechnology. The preceding "Nano" is a term from Greek that refers to "dwarf" [6]. Nanoparticles (NPs), which typically have dimensions between 1 and 100 nanometers (nm), are unique from their bulk counterparts. Their unique physicochemical, optical, and biological properties can be tailored to suit specific applications [7]. By utilising nanomaterials, nanotechnology has opened a new chapter in the treatment of wound healing by offering strategies for accelerating wound healing. The drug could be produced at a nanoscale to function as a self-contained "carrier," or nanomaterials could be used as drug delivery vehicles [8]. The primary types of nanomaterials utilized in wound therapy include scaffolds, coatings, nanocomposites, and nanoparticles. Because of its beneficial effects on treating and preventing bacterial infections, as well as speeding

up wound healing, metallic nanoparticles are becoming a more popular kind of nanomaterial. Additional advantages include low frequency of dressing changes, ease of use, and a continuous moist wound environment [9]. Silver NPs (AgNPs), gold NPs (AuNPs), and copper NPs (CuNPs) are examples of metal-based NPs with antimicrobial and wound-healing properties that have been reported. In addition, metal oxide NPs such zinc oxide NPs (ZnO NPs), titanium dioxide (TiO₂), cerium oxide (CeO₂), yttrium oxide (Y₂O₃), etc. Among these, silver nanoparticles draw a lot of attention due to their remarkable qualities, which include their large surface area to volume ratio, low tendency to develop resistance, and exceptional antimicrobial activity and wound healing properties. According to published reports, silver nanoparticles can regulate the release of anti-inflammatory cytokines and promote quick healing while minimizing scarring. Through keratinocyte proliferation, they also contribute to epidermal re-epithelization [10]. The synthesis of nanoparticles has generally been accomplished through the use of three distinct methodologies: chemical, biological, and physical. To overcome the shortcomings of physical and chemical methods, biological methods have emerged as feasible options. Biologically mediated synthesis of nanoparticles is a simple, cost-effective, dependable, and environmentally friendly approach using various biological sources like bacteria, fungi, plant extracts, and small biomolecules like vitamins and amino acids [11]. These biological sources contain active compounds, such as enzymes, proteins, polyphenols, flavonoids, and terpenoids, which can act as catalysing, reducing, stabilising, or capping agents for one-step synthesis [12]. The other advantages of biological methods are the availability of a vast diversity of biological resources, a decreased time requirement, high density, stability, and the ready solubility of prepared nanoparticles in water. Moreover, biological methods allow for additional proficiency in the control of shape, size, and distribution of the produced nanoparticles by optimization of the synthesis methods, including the number of precursors, temperature, pH, and the amount of reducing and stabilising factors [11].

The synthesis of AgNPs was reported in several studies through biological methods using *Turmeric extract* [13], *Arnebia nobilis root extract* [14], *Catharanthus roseus* and *Azadirachta indica extracts* [15], *Glucuronoxylan (GX) isolated from seeds of Mimosa pudica (MP)* [16]. Like the above plants, *Ficus lacor* is one such plant that is traditionally known for its great medicinal values. *Ficus lacor* Linn. as shown in fig. 1 is a large, fast-growing foliaceous, deciduous tree. It is about 20 metres tall and has a finely shaped crown. It is widely distributed throughout tropical and subtropical regions of the world. It is available globally in Southeast Asia, Australia, India, Myanmar, Bhutan, Nepal, and Burma/Indochina. Due to its diverse chemical composition, it has long been utilised as a treatment for a wide range of illnesses, including dysentery, hay fever, typhoid, ulcers, wounds, and gastric issues [17].



Fig. 1: *Ficus lacor* plant leaves

Table 1: Plant profile of *Ficus lacor* [17]

Kingdom	Plantae
Sub Kingdom	<i>Tracheobiota</i>
Super division	<i>Spermatophyta</i>
Division	<i>Magnoliophyta</i>
Class	<i>Magnoliopsida</i>
Subclass	<i>Hamamelidae</i>
Order	<i>Urticales</i>
Family	<i>Moraceae</i>
Genus	<i>Ficus</i>
Species	<i>Ficus lacor</i>

Plaksha (*Ficus lacor*) is mentioned as having potential wound-healing properties in ancient literature, such as Bhavprakash nighantu, Charak Samhita, and Sushrut Samhita. Acharya Charaka has written about using it externally on a variety of wounds, including ulcers that don't heal. The majority of the time, wound infections on human skin are caused by aerobic, anaerobic, Gram+ve (*S. pyogenes*, *S. aureus*), Gram-ve (*P. aeruginosa*) microorganisms. The antibacterial properties of *F. lacor* bark have been demonstrated against *S. aureus* and *E. coli* [18]. Additionally, recently, pharmacological activities such as antioxidant, anti-inflammatory, anti-diabetic, and anti-arthritis properties have been reported. Phytochemical screening demonstrated that Alkaloids, tannin, flavonoids, saponins, phenolic compounds, sterols, glycosides, coumarins, triterpenoids, amino acids, and carbohydrates are abundant in plants and these compounds are essential for the synthesis of silver nanoparticles [12, 17].

As silver and *Ficus lacor* plants both are having good antimicrobial and wound healing properties, our objective is to prepare silver nanoparticles using *Ficus lacor* plant extract to enhance a wound-healing activity along with green synthesis benefits. So our aim of this study is to prepare a topical gel using the *Ficus lacor*-silver nanoparticles and evaluate its effectiveness in an animal excision wound model.

MATERIALS AND METHODS

Collection of plant

The leaves of *Ficus lacor* were gathered in January 2022 from the local areas of Pune and an identity and authentication were obtained for the plant specimen by Dr. Rajashekar, Taxonomist, Indian horticulture research centre, Bengaluru.

Preparation of plant extract

The freshly collected leaves were washed thoroughly in running water to take away the dirt and dust on the surface of the leaves. Then, they were kept drying under shade for 15-20 d. Later the dried plant leaves were crushed and made into a coarse powder. Then the extraction was carried out through the maceration process, where the aqueous and hydro-alcoholic extracts were taken by adding 25 g of leaves powder into each 250 ml of sterile water and 70% alcohol in two separate conical flasks and kept for 3-4 d with occasional stirring. After 3-4 d the plant extract was filtered and the plant liquid filtrate was collected as shown in fig. 2 and stored at 20 degrees Celsius in a tightly closed vessel for future use.



Fig. 2: Plant extraction procedure

Preparation of silver nanoparticles

A 1 mmol silver nitrate (AgNO_3) solution is made by dissolving 0.1699g of AgNO_3 in 1000 ml of water. 5 different concentrations of plant aqueous and hydroalcoholic extracts were taken 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, each mixed with 10 ml of 1 mmol AgNO_3 solution. Synthesis of silver nanoparticles was carried out in an ambient temperature where the plant extract was added dropwise to the AgNO_3 solution on the magnetic stirrer at 100 rpm, maintaining basic pH, room temperature. Then the mixed solution was incubated for 24 h at room temperature and kept in dark condition to prevent

agglomeration. Later the formation of silver nanoparticles was indicated by the colour shift from yellow to dark brown. Then they were analysed using UV-visible spectroscopy, the concentration which gave the highest peak was considered for the larger preparation of nanoparticles. Then the same above procedures followed for the bulkier preparation by adding 100 ml of aqueous extract to 250 ml of silver nitrate solution and 75 ml of hydroalcoholic extract to 250 ml of silver nitrate solution and obtained AgNPs were separated and cleaned by frequent centrifugation for 15 min at 5000 rpm. Then the liquid supernatant was disposed of, and pellets were dried and kept for additional inspection, as shown in fig. 3.



Fig. 3: Preparation, confirmation and separation of nanoparticle

Confirmation and characterization of silver nanoparticle

Visible colour confirmation

After 24 h of incubation, the solution of 1 mmol silver nitrate+5 different concentrations of plant extract (1, 2, 3, 4, 5 ml) turned to dark brown, indicating and confirming the formation of silver nanoparticles as shown in fig. 3.

UV-visible spectroscopy

The prepared nanoparticles were analysed using UV-spectrometer in the range of 350-700 nm. For aqueous extract, the (4 ml plant extract+10 ml 1 Mm AgNO3) sample gave maximum absorbance of 3.510 observed at wavelength 391.6 nm and for hydroalcoholic extract, the (3 ml plant extract+10 ml 1 Mm AgNO3) sample gave maximum absorbance of 4.00 observed at wavelength 398.8 nm and it remain constant for all higher concentrations. It confirmed that the peak for the sample is the characteristic of surface plasmon resonance of silver nanoparticles so

this concentration was utilised for further study.

Particle size distribution analysis

The particle size distribution was measured using a Malvern Nano ZS 90 (Malvern Instruments, UK) after appropriate dilution with double distilled water. The mean particle size and distribution were measured based on photon correlation spectroscopy (PCS), dynamic light scattering, (DLS) technique, which is a powerful and versatile tool for estimating the particle size distribution of fine-particle materials ranging from a few nanometres to several micrometres. Light scattering was measured at 25 °C and with an angle of 90 °. The particle size distribution is reported as a Polydispersity Index (PDI). The range for the PDI is from 0 to 1. The values closer to zero indicate the homogenous nature of the dispersion and those greater than 0.5 indicate the heterogeneous nature of the dispersion.

The results were found as Z-Average of 329.3 d. nm, PDI of 0.485 and intercept of 0.887.

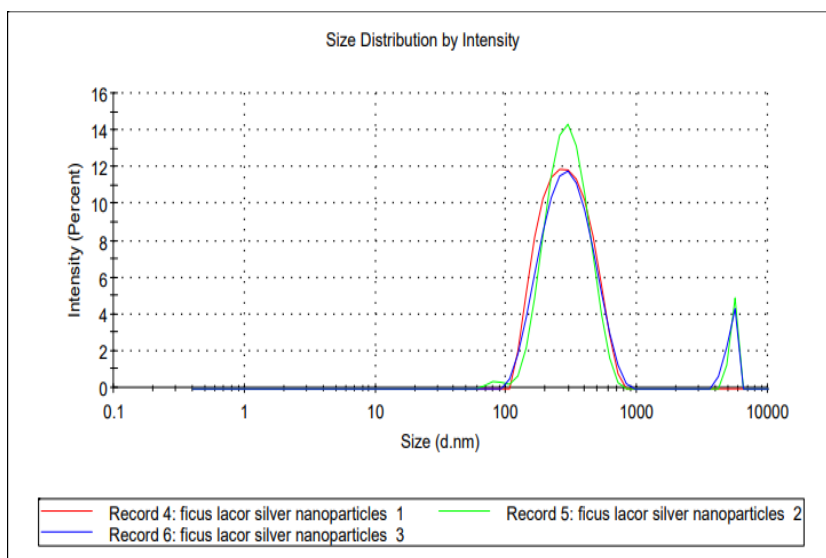


Fig. 4: Representing size distribution by intensity of ficus lacor-silver nanoparticles

Table 2: Showing size, % intensity, St Dev of ficus lacor-silver nanoparticles

Peak number	Size (d. nm)	% Intensity	St Dev (d. nm)
Peak 1	313.1	92.8	132.9
Peak 2	5193	7.2	478.8
Peak 3	0.000	0.0	0.000

In our studies, a PDI value of 0.485 indicates the homogenous nature of dispersion showing greater particle stability and the absence of aggregated nanoparticles. Z-Average value of 329.3 d nm indicating the average size of particle size distribution. Intercept of 0.887 indicating the data produced by the best system.

Preparation of topical nano gel

The topical *Ficus lacor*-silver nanoparticle-based gel was prepared using the carbopol 940 as a base. Where three different formulations were prepared using the 3 different concentrations of carbopol 940.

- 100 ml of distilled water with 0.5 g of carbopol 940 is Gel A (5%)
- 100 ml of distilled water with 0.75 g of carbopol 940 is Gel B (7.5%)
- 100 ml of distilled water containing 1.0 g of carbopol 940 is Gel C (10%)

The weighed amount of carbopol-940 was mixed with distilled water, gently stirred, and left for twenty-four hours to swell. After that, 12 g of glycerine is added, and triethanolamine is used to neutralise it until a transparent gel forms. The gel is then allowed to

stabilise for 24 h at room temperature. Using slow mechanical mixing (25 rpm) for 10 min, 1 ml of 169.9 µm/ml ethanol extract *Ficus lacor*-silver nanoparticles are finally added to 50 g gel to create the final formulation. Later, the homogeneity, consistency, pH, viscosity, and color of all three formulations were assessed.

Evaluation of the formulated gel

Physical examination and pH measurement

To ensure that the gel remained stable at the skin's pH of 5.5, the pH was also reassessed. Gel formulations were discovered to be homogenous, translucent, and odorous of ethanol. Table 6 illustrates that the gels' pH was below allowable bounds.

Rheological evaluation

Brookfield viscometer was used to determine the viscosity of prepared gels. The gels of 0.5, 0.75 and 1 gm were dissolved in 25 ml of purified water allowed to stand for 24 h then their viscosities were determined. The values showed that viscosity increased along with an increase in the concentration of carbopol-940 as shown in table 6.

Table 3: Showing results of evaluation parameters

Formulation	Homogeneity	pH	Viscosity (centipoises)
Gel A	Very good	7.0	7800
Gel B	Very good	7.5	7900
Gel C	Very good	7.5	8000

By the above evaluation of different formulations, the Gel A was found to give an ideal required properties so it was considered for further study.

Wound healing study in animal model

In the current investigation, albino wister rats weighing 150–180 g of either sex were employed. The Mallige College of Pharmacy's animal house provided the animals. The institutional animal ethical committee granted approval for the use of animals in experiments (Approval number: MCP 104/2021-22). According to the guidelines of the Committee for Control and Supervision of Experiments on Animals (CPCSEA), animals were kept in laboratory settings with regulated humidity and temperature. They will be provided with a standard water ad libitum.

Wound induction–excision wound model

The 12 rats were divided into 3 groups (standard, sample, gel base) each containing 4 rats. All rats were anaesthetised using ketamine hydrochloride (50 mg/kg i. p body weight) before creating a wound. Then the animal fur in the dorsum was shaved with a sterilised electric razor and after disinfection of the skin with Dettol liquid full-thickness, round wounds of 6 mm in diameter were excised under aseptic conditions with the help of a sterile dermal biopsy punch followed by marking the initial wound area by placing transparent polythene sheet then the area is measured by using millimetre based graph paper. Later the rat's wounds were bandaged to avoid infection.

Then, the formulations under study were applied daily to three

groups until the complete healing. (Group 1–standard drug silver nitrate gel [Silverex ionic, Sun Pharmaceutical Industries Ltd, Mumbai, India], Group 2–Test drug *Ficus lacor*-based silver nano gel, Group 3–gel base without active ingredient).

In this study, the effect of *Ficus lacor*-based silver nanogel activity will be evaluated by measuring wound contraction and epithelialization period. The wound area is measured and marked on days 0, 2, 4, 6, and 8 for all groups. Wound contraction was measured every 2nd day until complete wound healing and represented as a percentage of the healing wound area. Wound contraction was measured as percent contraction and was calculated using the below formula.

$$\% \text{ Wound contraction} = \frac{\text{Initial wound area} - \text{Specific day wound area}}{\text{Initial wound area}} \times 100$$

RESULTS

Excision wound model: wound healing activity

The effect of *Ficus lacor*-based silver nanogel activity on the excision wound model was evaluated by measuring wound contraction and epithelialization period. The wound area was measured and marked on days 0, 2, 4, 6, and 8 for all groups. Wound contraction was measured every 2nd d till 8th d and represented as a percentage of the healing wound area as shown in table 2 and the pictures wound healing shown in fig.

Table 4: Effect of ficus lacor-silver nanoparticles gel on animal excision wound model

Animal group	% Wound contraction on post wounding days			
	2 nd	4 th	6 th	8 th
Group 1 (Standard)	1.24±0.017	18.74±0.017	39.58±0	76.66±0
Group 2 (Sample)	1.24±0.04	19.16±0.01	37.91±0	76.24±0
Group 3 (Gel base)	0.41±0.02	14.58±0	33.75±0	58.33±0

(All values are represented as mean+/-SD)

The results showed that % wound contraction of Group 1 (standard) rats was 1.24% to 76.66%, Group 2 (sample) rats was 1.24% to 76.24%, Group 3 (gel base) rats was 0.41% to 58.33%

from day 2 to day 8.

The obtained data indicated that Group 1 (treated with silver nitrate

gel) and 2 (treated with *Ficus lacor*-silver nano gel) showed almost similar wound healing activity with a difference of 0.42% and the

group 3 treated with gel base alone showed lesser wound healing activity than group 1 and 2.

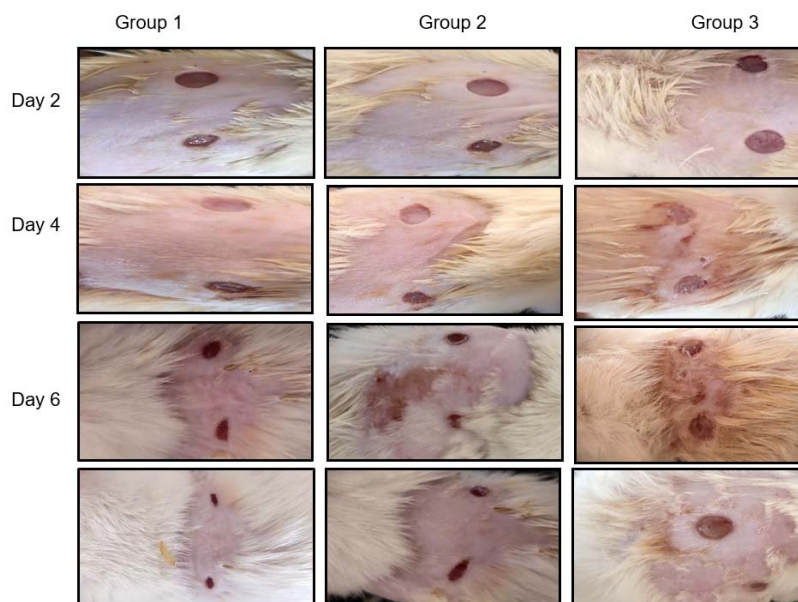


Fig. 5: Photographs of wound repair at different time interval in excision wound model in rats

DISCUSSION

Our study aimed to synthesise silver nanoparticles using *Ficus lacor* leaf extract to enhance wound healing with the advantages of green synthesis. We successfully prepared the nanogel and examined its effects on excision wounds. The production methods were meticulously selected from various studies, and our results demonstrated that the *Ficus lacor*-based silver nanoparticle gel was comparable in wound healing activity to a standard marketed product. Remarkably, Group 1 (treated with silver nitrate gel) and Group 2 (*Ficus lacor*-silver nanogel) exhibited almost identical wound healing activity, differing by just 0.42%. In contrast, Group 3, treated with gel base alone, showed inferior wound healing activity. The similarity in effectiveness between *Ficus lacor* silver nanoparticle gel and the standard product underscores the potential of green synthesis in wound healing solutions.

Whereas the studies conducted by Roy P Kr et al. on *Picrasma javanica* extract silver nanoparticles for wound healing activity [19] showed that the formulated plant extract nanogel exhibited enhanced wound healing activity than the standard used in study.

The *Ficus lacor*-silver nanogel offers advantages over silver nitrate, such as being environmentally friendly, biocompatible, and derived from a natural source, potentially reducing adverse effects when applied to wounds. The natural nanoparticles from *Ficus lacor* may have a broader spectrum of activity and reduced chances of bacterial resistance. Additionally, the plant extract may provide bioactive compounds for tissue regeneration and inflammation reduction.

The study has a few limitations that need to be mentioned. Due to budget constraints, comprehensive nanoparticle characterization using methods like FTIR, SEM, and XRD was not possible. The focus on a single wound model, the excision wound model, might not encompass the full range of wound healing effects. Histopathology parameters were not considered, which could have provided tissue-level insights. Gender-specific analysis was omitted, potentially overlooking gender-based variations. Preliminary phytochemical screening was not conducted, missing valuable information about plant extract constituents.

In light of these limitations, future research can address these issues by thoroughly characterizing *Ficus lacor*-silver nanoparticles, exploring various formulations, and expanding the scope to include a wider range of wounds and experimental models. Comparative

studies against existing herbal wound healing preparations can highlight unique advantages. These future directions hold promise for advancing our understanding of *Ficus lacor*-silver nanoparticles' applications in wound healing and related fields.

CONCLUSION

With passing years, the burden of wounds is increasing due to the rise in treatment costs and antimicrobial resistance. Within available treatment options, nanotechnology is found to have greater benefits, especially metallic nanoparticles prepared using biological methods have overcome many existing problems. Silver and *Ficus lacor* both are traditionally well-known for their ability to heal wounds, but the effect of green synthesised silver nanoparticles using the *Ficus lacor* on wound healing was not studied. Therefore in our present study, we demonstrated the wound healing activity of green synthesised *Ficus lacor*-silver nanoparticles topical gel on an animal excision wound model where the study drug *Ficus lacor*-silver nanogel exhibited similar wound healing activity in comparison with standard marketed product hence we can conclude that *Ficus lacor*-silver nanogel has the potential to be a good fit for wound healing.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The author declares no conflict of interest.

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