MODIFIED XANTHAN GUM-BASED GEL OF CURCUMIN AND COPPER NANOPARTICLES PREPARED FROM *TINOSPORA CORDIFOLIA* FOR WOUND THERAPY

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ABSTRACT

The aim. *The synthesis of nanoparticles through green methods is a biologically safe, cost-effective and environmentally friendly approach. This study focuses on the green synthesis of copper nanoparticles using aqueous stem extract of Tinospora cordifolia. Additionally, this research explores the formulation of an acetyl amine-modified xanthan gum-based gel incorporating curcumin and a solution of Cu^{++} nanoparticles, and investigates its wound healing activity.*
Materials and methods. *The shade-dried stem of Tinospora cordifolia was extracted with distilled water, which serves as a bio-reducing agent for the synthesis of Cu^{++} nanoparticles. Copper sulphate was added to the extract at room temperature using a magnetic stirrer. The visual color change during the addition indicates the formation of nanoparticles, which was further confirmed by UV spectroscopy and particle size analysis. The modified xanthan gum-based gel formulation was prepared using curcumin and a solution of Cu^{++} nanoparticles, and its wound healing activity was evaluated using the excision method, along with antimicrobial activity assessed by the cup and plate method.*
Results and discussion. *UV absorption was observed at 261 nm, and the particle size was measured at 188 nm, confirming the formation of nanoparticles. The gel containing curcumin and Cu^{++} nanoparticles was prepared using modified xanthan gum. The nanocomposite exhibited significant antimicrobial activity against gram-positive bacteria compared to gram-negative bacteria. The group treated with the modified xanthan gum-based curcumin and nano copper composite demonstrated significant wound closure by day 16±2.*
Conclusion. *The synthesis of Cu^{++} nanoparticles using Tinospora cordifolia and the formulation of a gel with modified xanthan gum and curcumin as a drug were successfully achieved. The gel formulation demonstrated significant antibacterial and wound healing activities, attributed to synergistic effect of Tinospora cordifolia, curcumin, and Cu^{++} nanoparticles.*

Key words: *Tinospora cordifolia, copper nanoparticles, modified xanthan gum, nanogel and antimicrobial agents, wound healing activity*

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ИСПОЛЬЗОВАНИЕ ГЕЛЯ НА ОСНОВЕ МОДИФИЦИРОВАННОЙ КСАНТАНОВОЙ КАМЕДИ С КУРКУМИНОМ И НАНОЧАСТИЦАМИ МЕДИ, ПОЛУЧЕННЫМИ ИЗ *TINOSPORA CORDIFOLIA*, ДЛЯ ЛЕЧЕНИЯ РАН

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РЕЗЮМЕ

Цель. *Синтез наночастиц с использованием зелёных методов является биологически безопасным, экономически эффективным и экологически чистым подходом. Данное исследование сосредоточено на зелёном синтезе медных наночастиц с использованием водного экстракта стебля Tinospora cordifolia. Кроме того, в рамках исследования была разработана формула геля на основе ксантановой камеди, модифицированной ацетиламином, которая включает куркумин и раствор наночастиц* Cu^{++}*, а также исследуется его ранозаживляющая активность.*

Материалы и методы. *Высушенный в тени стебель Tinospora cordifolia был экстрагирован дистиллированной водой, которая служит биовосстановителем для синтеза наночастиц* Cu^{++}*. К экстракту при комнатной температуре с помощью магнитной мешалки добавляли медный купорос. Визуальное изменение цвета во время добавления указывает на образование наночастиц, что было дополнительно подтверждено данными УФ-спектроскопии и анализом размера частиц. Модифицированная формула геля на основе ксантановой камеди была приготовлена с использованием куркумина и раствора наночастиц* Cu^{++}*, её ранозаживляющая активность была оценена с помощью метода иссечения, а антимикробная активность – методом диффузии в агаре.*

Результаты и обсуждение. *Поглощение УФ-излучения было зафиксировано при 261 нм, а размер частиц измерялся при 188 нм, что подтверждает образование наночастиц. Гель, содержащий куркумин и наночастицы* Cu^{++}*, был приготовлен с использованием модифицированной ксантановой камеди. Нанокомпозит проявил значительную антимикробную активность в отношении грамположительных бактерий по сравнению с грамотрицательными. Группа, получавшая лечение модифицированным композитом на основе куркумина, ксантановой камеди и наномедных частиц, продемонстрировала значительное закрытие ран к 16 ± 2 дню.*

Заключение. *Успешно осуществлён синтез наночастиц* Cu^{++} *с использованием Tinospora cordifolia и разработан гель с модифицированной ксантановой камедью и куркумином с возможностью его применения в качестве лекарственного средства. Гель продемонстрировал значительную антибактериальную и ранозаживляющую активность, обусловленную синергетическим эффектом компонентов: Tinospora cordifolia, куркумина и наночастиц* Cu^{++}*.*

Ключевые слова: *Tinospora cordifolia, наночастицы меди, модифицированная ксантановая камедь, наногель и антимикробные агенты, ранозаживляющая активность*

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INTRODUCTION

Overuse or non-selective use of antibiotics has resulted in a global rise in multidrug resistance among various microorganisms. Currently, more than 2 million people are suffering from infections caused by resistant strains of microorganisms, and experts predict that by 2050 there will be approximately 10 million deaths annually worldwide [1]. Therefore, new, broad-spectrum and selective antimicrobial alternatives are needed to combat multidrug-resistant strains [2]. The emergence of resistance in different bacterial strains to various antimicrobial agents is attracting a lot of attention for the development of new drug treatments.

Nanotechnology is a field of science with vast applications in various areas, including chemical industries, the biochemical field, cosmetics industries, electronic and energy sciences, food industries, and space industries. It also plays a significant role in healthcare and pharmaceutical industries [3]. Metal nanoparticles are considered as one of the most promising approaches in all these areas [4]. Nanoparticles can be synthesized using both physical and chemical methods, but they suffer from drawbacks such as hazardous reaction conditions, excessive reagents, longer times and tedious isolation processes. Therefore, it is necessary to develop new methods for synthesising nanoparticles (NPs) that require milder conditions, inexpensive reagents and an environmentally friendly approach [5]. The development of metal nanoparticles using biological materials has attracted significant attention due to their safety, biocompatibility, cost-effectiveness, and environmental friendliness. It has been reported that metal nanoparticles (Ag^{++}, Cu^{++}, Au^{++}, and Zn^{++}) exhibit a wide spectrum of antimicrobial activity against different species of microorganisms [6].

Among the nanoparticles, copper nanoparticles (Cu-NPs) have gained much attention due to their low cost of preparation, wide availability, excellent physical and chemical properties, and antibacterial activity against a variety of bacteria and fungi [7]. Cu-NPs were synthesized by various methods, including vapor deposition, electrochemical reduction, thermal deposition, radiolytic reduction, chemical reduction, and green synthesis [8]. Green synthesis can also be achieved using microorganisms or plant extracts [9]. It has been found that, plant extracts prepared using green synthesis methods can stabilize nanoparticles. Various plant extracts have been used for synthesizing Cu-NPs, including citrus lemon fruit [10], *Ocimum sanctum*, *Rhus coriaria L.* fruits [11], *Ageratum houstonianum* [12] Madhunashini [13], tea [14], *Avrevalanta* [15], *Eclipta prostrata* [16], *Tinospora cordifolia* [17], *Arachis hypogaea* [18], *Mentha spicata* [19], coriander [20], etc. Due to their high surface-to-volume ratio, Cu-NPs are highly reactive and can easily interact with other particles, increasing their antimicrobial efficacy. The mechanism of Cu-NP killing microorganisms is multifaceted and is not fully understood. However, literature suggests that nanocopper interacts with phosphorus- and sulphur-containing biomolecules such as DNA and proteins, distorting their structures and disrupting biochemical processes [21]. Nanocopper also interacts with microorganisms on different cellular levels, leading to cell death [22, 23].

The mechanisms of wound healing are still not fully understood, making it one of the most challenging areas of medicine. Wound healing refers to the process of repairing damaged skin or tissue. An essential component of wound management is the use of antimicrobial agents to control microbial growth in the wound area. Copper nanoparticles possess several beneficial properties for promoting wound healing, such as antibacterial, antifungal, antiviral, and anti-inflammatory effects. Curcumin, a traditional herbal remedy, has shown promising potential as a novel therapeutic option for wound healing due to its multiple activities, including antibacterial, anti-inflammatory, and antioxidant properties [24].

This study is focused on developing a safe and effective treatment for antimicrobial and wound healing based on the combination of curcumin and copper nanoparticles. To achieve this, the effect of a curcumin-nano-copper composite was compared to a standard formulation. Acetylamine-modified xanthan gum (MXG) was used to enhance the gelation properties of xanthan, which was then used in the preparation of a gel formulation. This gel formulation included the preparation of copper nanoparticles (Cu^{++}-NPs) using a green method with a bio-reducing agent such as the aqueous extract of *Tinospora cordifolia*. The prepared Cu^{++}-NP was analysed using UV spectroscopy and particle size analysis to determine its properties. The antimicrobial properties of the MXG-based Cu^{++}-NP gel containing ciprofloxacin were also determined. This study observed the potential of combining these two substances to create a synergistic effect that could lead to a more effective treatment than using them individually. The results obtained through practical research can contribute to expanding the range of available medications for the treatment of skin conditions caused by various pathogens.

MATERIALS AND METHODS

All synthetic chemicals and the ciprofloxacin drug were purchased from local distributors. Modified xanthan gum was produced in the laboratory. All other chemicals used were of analytical reagent quality. Curcumin was obtained as a gift sample from Satara Arkshala (Satara, India).

Preparation of the extract

From the collected plant *Tinospora cordifolia*, the stems were separated, washed with distilled water and kept in the shade for 10–15 days to dry. After drying, 10 g of chopped stems were boiled in 100 mL of distilled water at 80°C for 1 hour. The resulting filtrate was used to prepare copper nanoparticles.

Green synthesis of copper nanoparticles using the *Tinospora cordifolia* stem extract

A stem extract (10 mL) was added to a 0.01 M copper sulphate solution (100 mL), and a mixture was stirred continuously for 30 minutes. During this time, the light sky-blue colour of the solution changed to a yellowish-green colour, indicating the formation of copper nanoparticles. After this process, the solution was placed in an incubator for 24 hours, and then filtered through Whatman filter paper [25].

Characterization of Cu^{++} nanoparticles

UV-visible absorption spectra of copper nanoparticle solutions were taken over the wavelength range of 200 to 800 nm using a UV-Visible spectrophotometer (Shimadzu Corp., Japan).

The particle size and zeta potential of a solution containing Cu^{++} nanoparticles were analyzed by HORIBA SZ-100 particle size analyzer (Horiba Ltd., Japan).

Preparation of the modified xanthan gum-based gel

Acetylamine modification was prepared by reacting xanthan gum with chloroacetyl chloride and further treating it with ammonia to enhance the gelling properties of the original xanthan gum. 100 mg of MXG was dissolved in 10 mL of Cu^{++}-NPs solution, along with 0.2 mL of glycerin, and stirred to form MXG-based Cu^{++}-NPs [26].

Physiochemical evaluation of the gel

The viscosity of the gel was measured using a Brookfield viscometer with a spindle L4 at a speed of 100 rpm. To assess its spreadability, a formulated gel (1 mg) was placed between two glass slides, and a definite amount of weight was applied to the glass side. A definite force was then applied to the movable slide so that the gel spread, and the spreadability index was measured.

$$\text{Spreadability} = \text{Weight tied} \times \frac{\text{Length of silde}}{\text{Time in second}}$$

Antimicrobial evaluation

The antimicrobial activity of a modified xanthan gum-based Cu^{++} nanoparticles gel containing curcumin was assessed against *E. coli* (gram-negative) and *Bacillus subtilis* (gram-positive) bacteria using a previously reported method [27]. Bacterial strains were obtained from the Department of Microbiology (GIPER, India). In this study, Ciprofloxacin (5 µg/mL) was used as positive control. Antimicrobial activity of the gel was measured using the agar diffusion assay.

In a sterile environment, gram-positive and gram-negative bacteria were cultivated on agar plates. All solutions (0.1 mL) were placed in the cups of agar plates, and the plates were incubated at 37 °C for 24 hours. After incubation, the plates were observed for microbial growth. All measurements were done in triplicate for each organism, and an average diameter was noted in the form of a zone of inhibition.

Wound healing activity

The wound healing activity was evaluated using the previously described method, by excising a wound model in adult albino rats weighing 150–160 g [28]. The animals were numbered and then divided into three groups with six animals each. Group 1 was the control group and received no treatment. Group 2 was treated with the standard drug formulation. Group 3 was treated with modified xanthan gum-based nanogel.

Using an electric clipper, the dorsal fur of anaesthetized animals was shaved. A wound was created on the back of animals in the inter scapular region, 5 mm away from the ear. The demarcated area was excised to create a wound with a diameter of 2 cm. Wound area was measured on days 0, 2, 4, 8, 12, 16, 18, 20, 22, and 24 by counting the number of squares on graph paper that covered the retraced wound. The degree of wound closure was calculated using a formula as a percentage of the original wound area:

$$\% \text{ Closure} = 1 - \frac{\text{Wound area on corresponding days}}{\text{Wound area on day zero}} \times 100$$

RESULTS AND DISCUSSION

The formation of copper nanoparticles has been confirmed by changes in colour and UV spectroscopy. When copper nanoparticles form, the colour of the solution changes from light sky-blue to yellowish green.

UV visible spectroscopy

UV-Vis spectral analysis of Cu^{++} NPs was conducted in the wavelength range of 200–800 nm. The peak at 261 nm confirmed the formation of Cu^{++} NPs. Figure 1 shows the UV spectra, which demonstrates absorption at 261 nm.

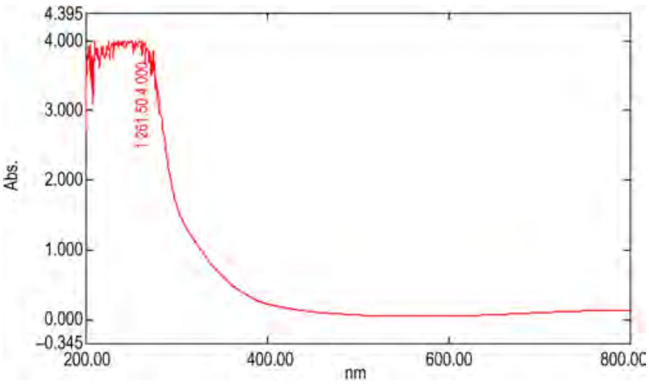

FIG. 1.
UV spectra of copper nanoparticles prepared from Tinospora cordifolia stem extract

Particle size analysis (PSA)

Particle size determination is helpful for analyzing nanoscale systems. The size of Cu^{++} nanoparticles was determined using a HORIBO SZ-100 particle size analyzer. The average size was found to be 188.1 nm (Fig. 2), indicating the formation of a nano copper particle system.

The zeta potential of the prepared Cu^{++}NPs was found to be –21.9 mV. This value indicates that prepared Cu^{++}NPs have sufficient charge and mobility to inhibit aggregation.

Physiochemical evaluation of the formulated gel

The nanogel formulation had a yellowish-green colour and good consistency. It was transparent in appearance. Viscosity measurements were conducted using a Brookfield viscometer, and the range was 600–650 cps at 100 rpm, using the L4 spindle. The viscosity of the nanogel was 615.6 ± 9.704 cps. These viscosity values met the requirements for a gel, compared to a standard gel. The spreadability values indicate that the gel can be easily spread. The spreading diameter of the prepared gel ranged from 23 to 35 mm.

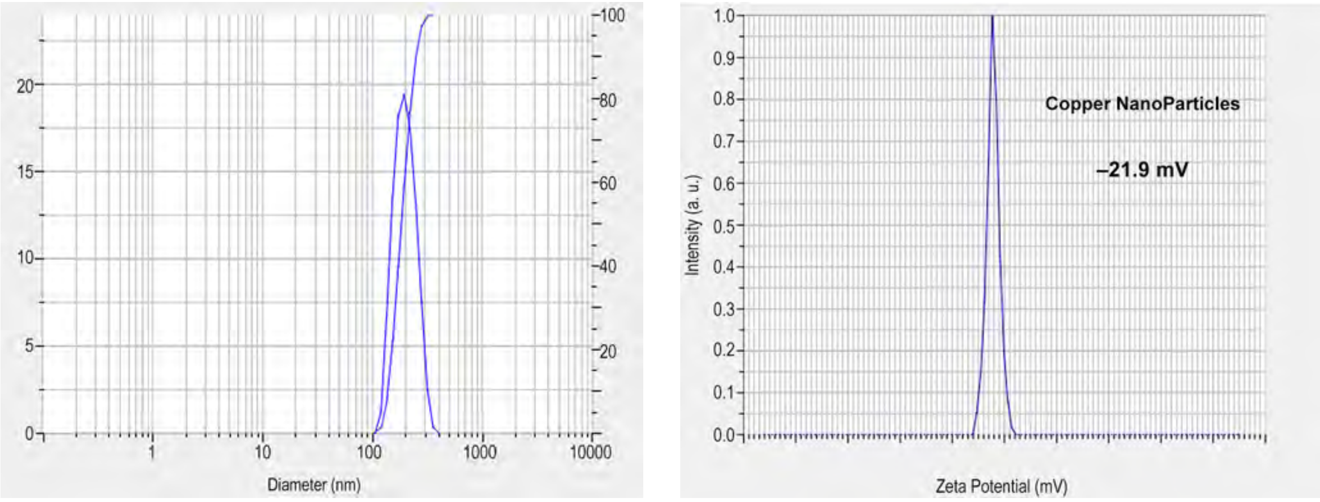

FIG. 2.
Particle size analysis and zeta potential of copper nanoparticles

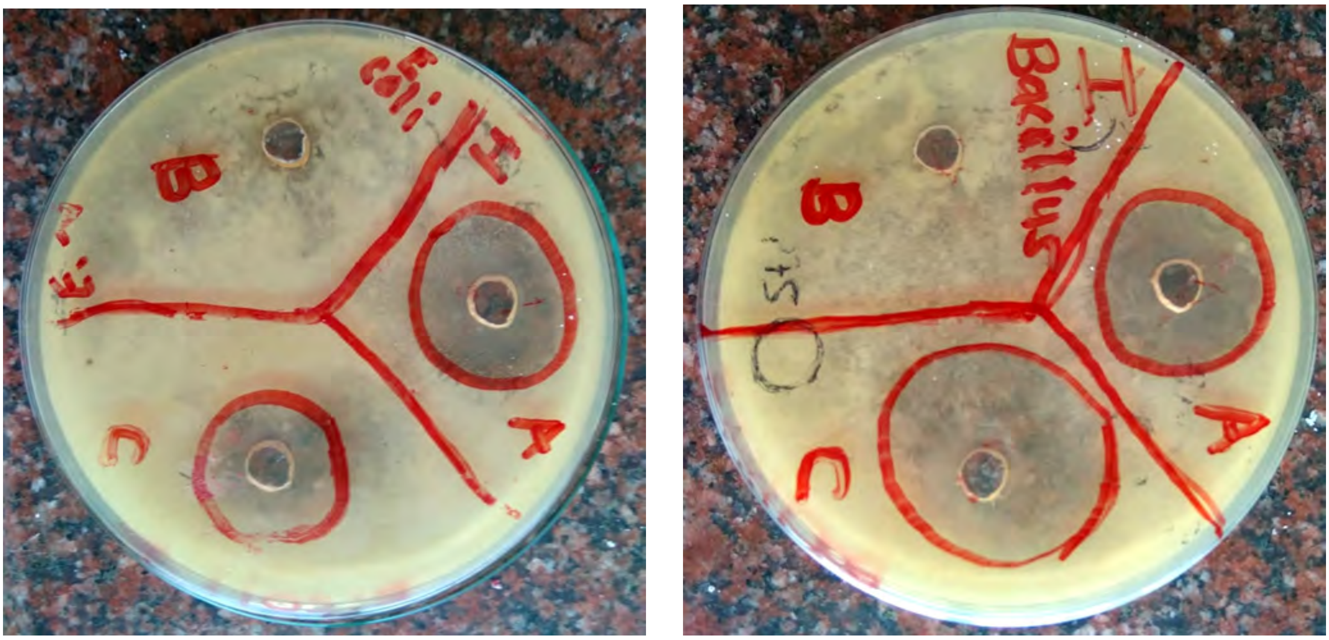

FIG. 3.
Zone of inhibition of ciprofloxacin standard (A), blank (B) and curcumin-Cu^{++}NPs hydrogel (C)

Antimicrobial activity of MXG gel containing curcumin-Cu^{++} nanoparticles

The curcumin nanoparticles were tested for their antibacterial properties against gram-positive strains (*Bacillus subtilis*) and gram-negative strains (*E. coli*). The results are shown in Figures 3 and 4.

The antibacterial effect of curcumin-Cu^{++}NPs has been found to be more pronounced against gram-positive bacteria as compared to the standard. Several studies have shown that curcumin is more effective against various *Bacillus subtilis* strains [29]. Significant antibacterial activity against *B. subtilis* can be attributed to the presence of both curcumin and copper nanoparticles in the formulation, which are well-known and effective antibacterial agents.

It has been predicted that Cu^{++}NPs can join the microbial cell surface and enter the cell, where they can disturb intracellular targets, including respiratory catalysts [20]. Curcumin-Cu^{++}NPs have also shown equivalent antibacterial activity against gram-negative *E. coli* strains compared to the standard.

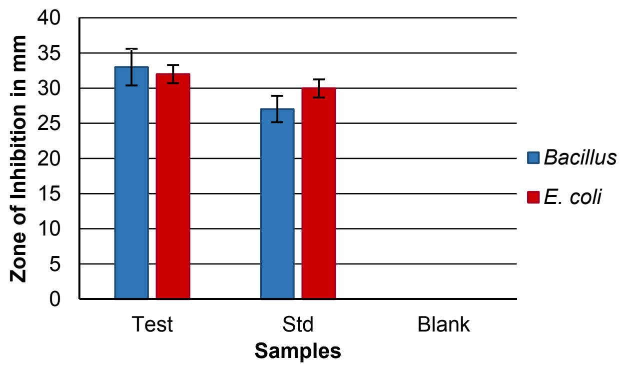

FIG. 4.
Antibacterial activity of nanogel against Bacillus subtilis and E. coli strains (n = 3)

Wound healing activity

The wound healing effect of curcumin-Cu^{++}NPs was investigated in a 2×2 cm excisional skin wound model. Standard iodine-povidone cream and MXG-based curcumin-Cu^{++}NP gel were applied every 24 hours. The rate of wound healing based on the appearance and diameter of the wound was evaluated in comparison to positive and negative controls. After day 6, the wound closure rate was significantly faster in Groups 2 (standard treatment) and 3 (curcumin-Cu^{++}NPs gel) animals. After days 15–16, the curcumin-Cu^{++}NPs showed complete wound closure, while standard treated animals took 18–19 days to achieve complete wound closure.

Curcumin is well known for its antimicrobial and wound-healing properties. Due to its antioxidant activity, curcumin has the ability to neutralize reactive oxygen species and prevent lipid peroxidation at the wound site [30]. In addition, it promotes cellular proliferation, collagen synthesis and maturation, as well as extracellular matrix biosynthesis in the wound area. However, curcumin has a low bioavailability, and it is unstable in neutral and alkaline aqueous solutions. These drawbacks can be overcome by using a nanoparticle formulation, which allows for the gradual release of the compound, and shows significant activity compared to the standard formulation. The combination of curcumin with Cu^{++}NPs enhances wound healing activity even more than the standard iodine povidone gel or negative control. Figures 5 and 6 show the wound healing results compared to standard treatment and controls.

The significant wound healing activity may be due to the additive or synergistic effects of curcumin and copper nanoparticles.

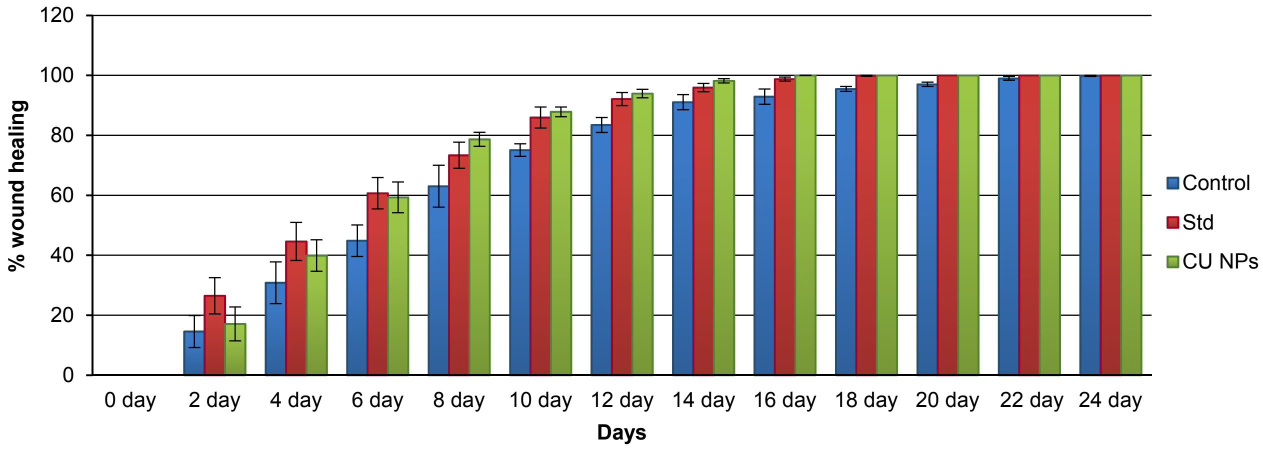

FIG. 5.

Wound healing activity of Cu^{++}-NPs gel as compared to standard and control form (n = 6, Me ± SD)

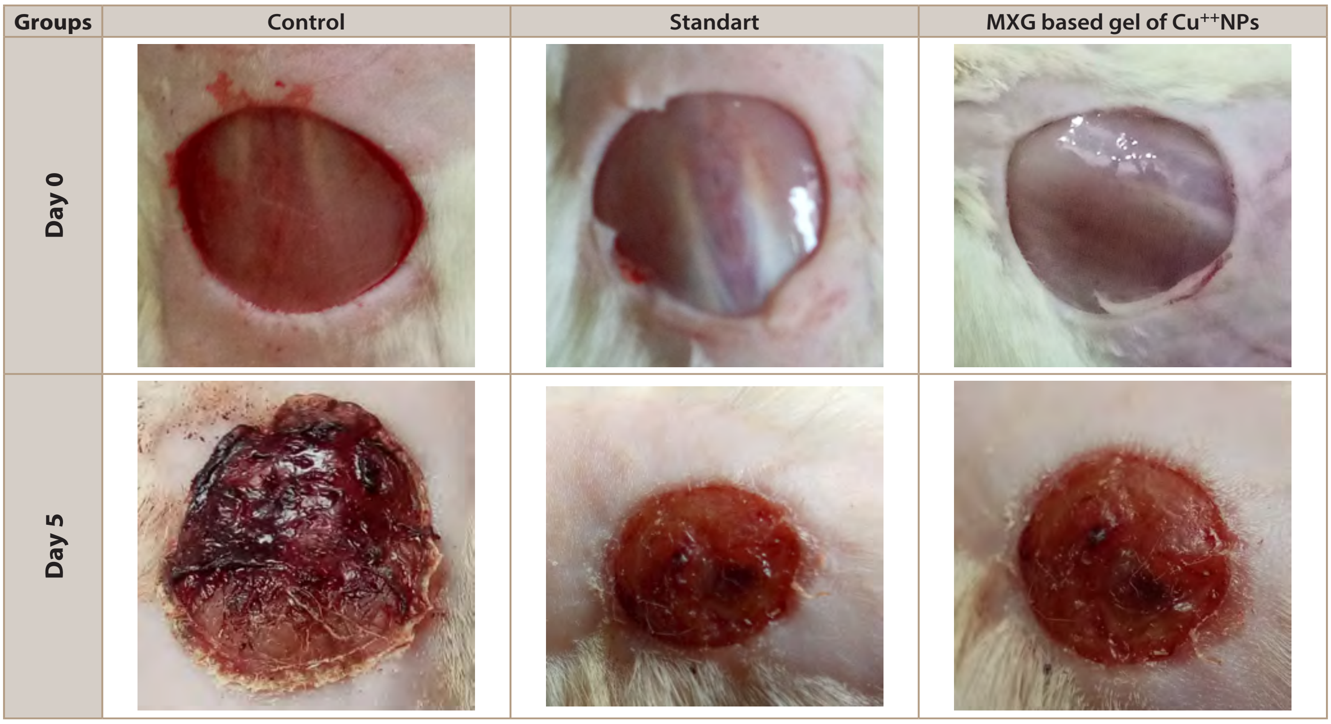

FIG. 6.

Photographs of wound healing activity of curcumin-Cu^{++}NPs gel as compared to standard and controls. The images show the wound surface healing over time in each group (n = 6)

FIG. 6. *(continued)*
Photographs of wound healing activity of curcumin-Cu^{++}NPs gel as compared to standard and controls. The images show the wound surface healing over time in each group (n = 6)

CONCLUSION

Thus, it can be concluded that a gel formulation using modified xanthan gum as a gelling agent and Cu^{++} nanoparticles prepared from *Tinospora cordifolia* has been successfully developed. This gel shows significant antibacterial and wound-healing activities. It exhibits stronger antibacterial activity against *Bacillus subtilis* than against *E. coli*. The gel with bio-synthesized Cu^{++} nanoparticles and curcumin could be used as an effective therapeutic agent for wound treatment with increased wound-healing efficacy. The formulation exhibits strong antibacterial and wound-healing effects due to the synergistic or additive actions of *Tinospora cordifolia*, curcumin, and Cu^{++} nanoparticles.

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Conflict of interest

Authors have declared no conflict of interests.

Ethical clearance

The protocol operated in this study regarding the use of albino rats as an animal model for acute oral and dermal toxicity was approved by the Institutional Animal Ethics Committee, GIPER (Limb, Satara, Maharashtra, India; protocol No. GIPER/IEC/2020-21/03 dated 27/01/2021). The animal study conducted in this work complies with NC3Rs guidelines.

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