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COPPER NANOPARTICLE-INCORPORATED PLATELET-RICH PLASMA (CUNP-PRP)FOR WOUND HEALING IN ACUTE AND CHRONIC WOUNDS: A PROSPECTIVE INTERVENTIONAL STUDY

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ABSTRACT

Background: Chronic and infected wounds remain a major clinical challenge because of delayed healing, microbial resistance, and impaired tissue regeneration. Platelet-rich plasma (PRP) promotes regeneration through concentrated growth factors but has limited intrinsic antimicrobial action, whereas copper nanoparticles (CuNPs) possess strong antimicrobial and pro-angiogenic properties. We hypothesised that a copper nanoparticle-incorporated PRP (CuNP-PRP)nanocomposite would combine both e fects.

Methods: This prospective interventional study enrolled patients with acute and chronic wounds at the Department of General Surgery, Saveetha Medical College and Hospital. Copper nanoparticles were synthesised by chemical reduction and combined with autologous PRP prepared by double centrifugation. Twenty patients completed the 8-week treatment and follow-up protocol. Wound healing was assessed by serial measurement of wound area; antimicrobial activity was tested in vitro by zone-of-inhibition assay against common wound pathogens; and cytotoxicity/biocompatibility were assessed on 3T3- L1 fibroblasts by MTT assay and phase-contrast morphology.

Results: The CuNP-PRP formulation showed broad-spectrum antimicrobial activity, greatest against Staphylococcus aureus (zone of inhibition 17.4± 2.1mm). Meanwound size fellfrom 6.46± 2.17cm2at baseline to 0.9 ± 0.31 cm2 at week 8 (86.1% reduction; paired t-test, $p<0.001$). Complete healing occurred in 60% of patients, with improvement in all cases and no non-healing wounds; healing did not di fer significantly by wound aetiology (χ2test, $p=0.61$). The formulationwaswelltolerated (85% no adverse efects)with high patient satisfaction (90.5% satisfied or highly satisfied). CuO nanoparticles showed dose-dependent cytotoxicity on fibroblasts, with >90% viability at 25–100µL/mL and significant decline at ≥200µL/mL ($p<0.05$).

Conclusion: CuNP-PRP demonstrated significant antimicrobial activity, accelerated wound closure, and good biocompatibility at appropriate doses, supporting its potential as a cost-effective adjunct for wound management, particularly in resource-limited settings. Larger randomised controlled trials with a comparator arm are warranted.

KEYWORDS: Copper nanoparticles; Platelet-rich plasma; Wound healing; Nanocomposite;Antimicrobial activity; Cyto toxicity; Diabetic foot ulcer

1. INTRODUCTION

Wound healing is a tightly coordinated biological process encompassing haemostasis, inflammation, proliferation, and tissue remodelling, all of which act in sequence to restore the structural and functional integrity of injured skin.1>2 Successful repair depends on adequate vascular supply, effective extracellular matrix formation, and control of microbial contamination.3 Diabetes mellitus, vascular insufficiency, persistent infection, and chronic inflammation frequently disrupt this sequence, producing non-healing wounds that are costly to treat and burdensome for patients.4 _ 6

Platelet-rich plasma (PRP), an autologous concentrate of platelets and growth factors obtained from centrifuged whole blood, has become a widely used regenerative therapy. On activation, platelets release platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and other cytokines that drive fibroblast proliferation, angiogenesis, and epithelialisation.7 _ 11 However, PRP alone provides little direct antimicrobial protection, which limits its effectiveness in colonised or infected wounds.12

Metallic nanoparticles, particularly copper nanoparticles (CuNPs), have attracted interest as antimicrobial and pro-angiogenic agents. Copper is a trace element essential for angiogenesis, collagen cross-linking, and antioxidant defence, and at the nanoscale it produces broad-spectrum antimicrobial effects through membrane disruption, reactive-oxygen-species generation, and interference with microbial protein and nucleic acid synthesis – a multi-target mechanism that makes resistance development less likely than with conventional antibiotics.13_ 16 Beyond infection control, CuNPs have also been reported to stimulate angiogenesis via the HIF- 1α–VEGF axis and to promote fibroblast proliferation and collagen deposition.17 _ 18

Combining CuNPs with PRP is therefore a rational strategy: PRP contributes regenerative growth factors, while CuNPs add antimicrobial and angiogenic support, potentially yielding a nanocomposite that outperforms either component used alone. Evidence directly evaluating a combined CuNP-PRP formulation, however, remains limited. We therefore designed a prospective interventional study to synthesise and characterise a CuNP-PRP formulation and to evaluate its antimicrobial efficacy, in-vitro biocompatibility, and clinical wound-healing performance in patients with acute and chronic wounds.

2. MATERIALS AND METHODS

2.1Study design and setting

This was a prospective interventional (single-arm) study conducted in the Department of General Surgery, Saveetha Medical College and Hospital, Chennai, over a one-year period. The study was registered with the Clinical Trials Registry – India (CTRI/2026/03/105841) and approved by the Institutional Ethics Committee of Saveetha Medical College and Hospital (IEC Ref. No. 024/09/2025/IEC/SMCH). The study was conducted in accordance with the Declaration of Helsinki and the Indian Council of Medical Research ethical guidelines for biomedical research on human participants. Written, bilingual (English/Tamil) informed consent was obtained from every participant prior to enrolment.

2.2Participants

Patients aged above 18 years, presenting with acute or chronic wounds of mild-to-moderate severity (including diabetic foot ulcers, surgical site infections, and traumatic wounds), and with no known hypersensitivity to copper compounds or plasma-derived products, were eligible. Patients with severe infection, extensive necrosis, gangrene requiring surgical intervention, copper hypersensitivity, or systemic illness likely to impair wound healing were excluded. Patients were recruited by consecutive convenience sampling from those attending the wound-care clinics and surgical units of the department. Thirty patients were screened; twenty patients who completed the full 8-week treatment and follow-up protocol were included in the final analysis reported here.

2.3 Preparation of copper nanoparticles and CuNP-PRP formulation

Copper nanoparticles were synthesised by a chemical reduction method: copper salt solutions were treated with reducing agents and stabilisers under controlled laboratory conditions to yield nanoparticles of consistent size and stability. Nanoparticle identity and stability were verified by UV-visible spectrophotometry and scanning electron microscopy. Autologous PRP was prepared from 10–20 mL of venous blood collected under sterile conditions and processed by a double-centrifugation technique: an initial slow spin separated plasma and platelets from red blood cells, and a second, faster spin concentrated the platelet fraction. The synthesised copper nanoparticles were then incorporated into the PRP under sterile conditions with gentle mixing to produce a uniform CuNP-PRP nanocomposite.

2.4 Clinical application and follow-up

Wounds were cleaned and debrided using standard wound-care technique before topical application of the CuNP-PRP formulation under sterile conditions, followed by a sterile dressing. Patients were reviewed at predetermined intervals over 8 weeks, at which wound size, granulation tissue, signs of infection, and adverse effects were assessed and documented. Primary outcomes were the rate of wound closure, percentage reduction in wound size, and time to complete healing; secondary outcomes were in-vitro antimicrobial effectiveness, improvement in tissue regeneration, and absence of adverse reactions.

2.5 In-vitro antimicrobial assay

Antimicrobial efficacy of the CuNP-PRP formulation was assessed in vitro by the standard zone-of- inhibition method against four common wound pathogens: Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae.

2.6 In-vitro cytotoxicity and cell morphology

Cytotoxicity of copper oxide nanoparticles (CuO NPs) was evaluated on 3T3-L1 mouse fibroblasts using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay. Cells were seeded at 5,000 cells/well in DMEM-F12 with 10% fetal bovine serum, exposed to CuO NP concentrations of 25–250 µL/mL for 24 hours, and assessed by absorbance at 570 nm following formazan solubilisation in DMSO; viability was expressed relative to untreated controls. Cell morphology at selected concentrations (100 and 200 µL/mL) was additionally examined by phase-contrast microscopy for evidence of shrinkage, rounding, or detachment.

2.7 Statistical analysis

Continuous variables are expressed as mean ± standard deviation and were compared using the paired t- test (or Mann-Whitney U test, where appropriate) for pre- and post-treatment comparisons. Categorical variables were compared using the chi-square test. A p-value <0.05 was considered statistically significant. Analyses were performed using standard statistical software.

3. RESULTS

3.1Demographic characteristics

Ofthe 20 patients analysed, the majority (40%)were aged46–60years, followed by 35% aged 31–45years, 15% aged 18–30 years, and 10%aged above60years (Table 1, Figure 1). Males comprised 60% ofparticipants andfemale40%.

Table 1. Age distribution ofstudy participants (n=20).

AGE	Number(n)	Percentage (%)
18–30years	3	15
31–45years	7	35
46–60years	8	40
>60years	2	10
Total	20	100

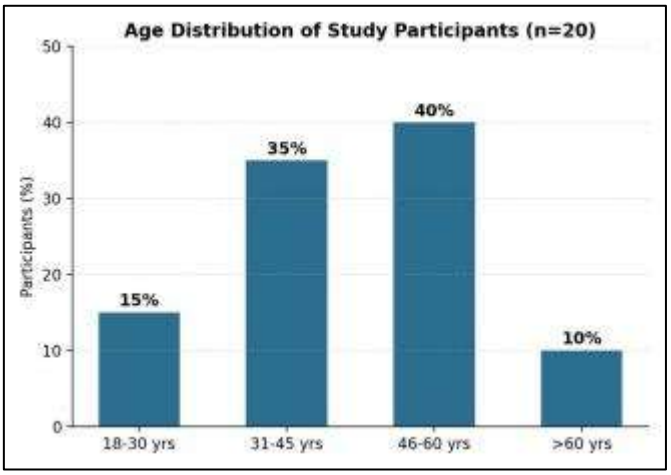


Figure 1. Age distribution ofstudy participants.

Table 2. Gender distribution ofstudy participants (n=20).

Gender	Number(n)	Percentage (%)
Male	12	60
Female	8	40
Total	20	100

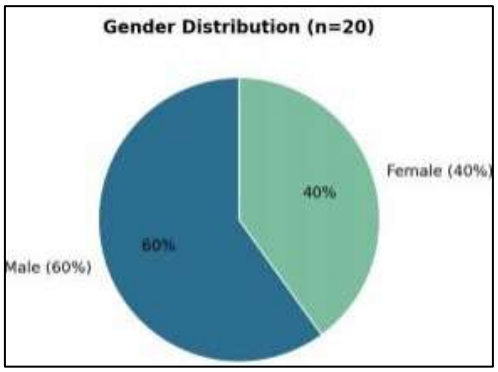


Figure 2. Gender distribution of study participants.

3.2Wound characteristics

Diabetic foot ulcers were the most common woundtype (70%), followed by surgical site infections (15%)and traumaticwounds(15%) (Table 3, Figure 3). At baseline, the mean wound duration was 6.03± 2.35weeks, mean wound size was 6.46 ± 2.17 cm2, mean wound depth was 4.43± 139mm, and mean pain score (VisualAnalogue Scale) was 634 ± 1.40, indicating a clinically significant burden of subacute-to-chronic wounds of moderate severity(Table 4, Figure 4).

Table 3. Distribution of wound types among study participants (n=20).

Type of Wound	Number(n)	Percentage (%)
Diabetic foot ulcer	14	70
Surgical site infection	3	15

Traumatic wound	3	15
Total	20	100

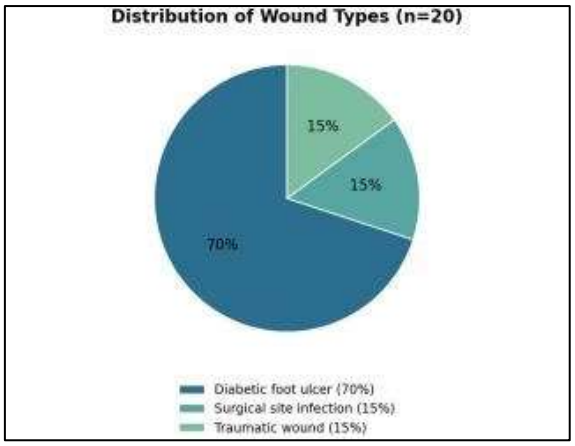


Figure 3. Distribution of wound types among study participants.

Table 4. Baseline wound characteristics of study participants (n=20).

Parameter	Mean ± SD
Woundduration(weeks)	6.03±2.35
Initial wound size(cm²)	6.46±2.17
Wounddepth (mm)	4.43 ± 1.39
Painscore(VAS, 0–10)	6.34± 1.40

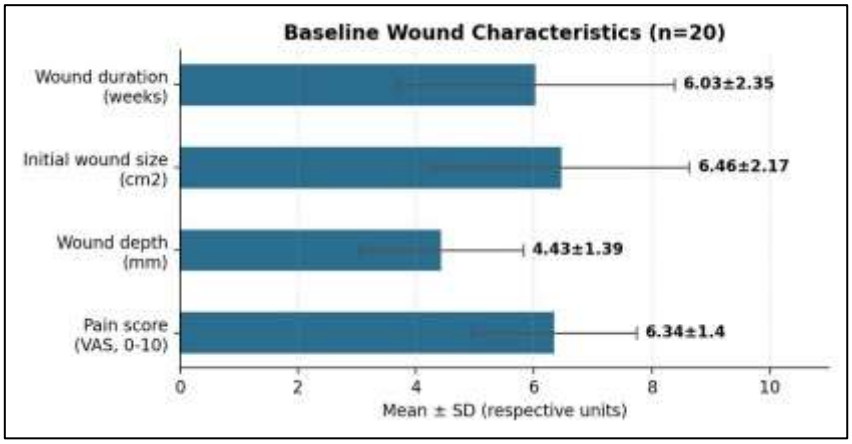


Figure 4. Baseline wound characteristics of study participants.

3.3 Antimicrobial activity

The CuNP-PRP formulation demonstrated broad-spectrum in-vitro antimicrobial activity against all four tested pathogens, with the largest zone of inhibition against Staphylococcus aureus (17.4 ± 2.1 mm), followed by Pseudomonas aeruginosa (16.2 ± 2.0 mm), Escherichia coli(15.6± 1.8 mm), and Klebsiella pneumoniae (14.9± 1.7mm)(Table 5, Figure 5).

Table 5. In-vitro antimicrobial activity of the CuNP-PRP formulation.

Microorgansm	Zone of Inhibition(mm), Mean ± SD
Staphylococcusaureus	17.4±2.1
Pseudomonasaeuginosa	16.2±2.0
Escherichia coli	15.6± 1.8
Klebsiella pneumoniae	14.9± 1.7

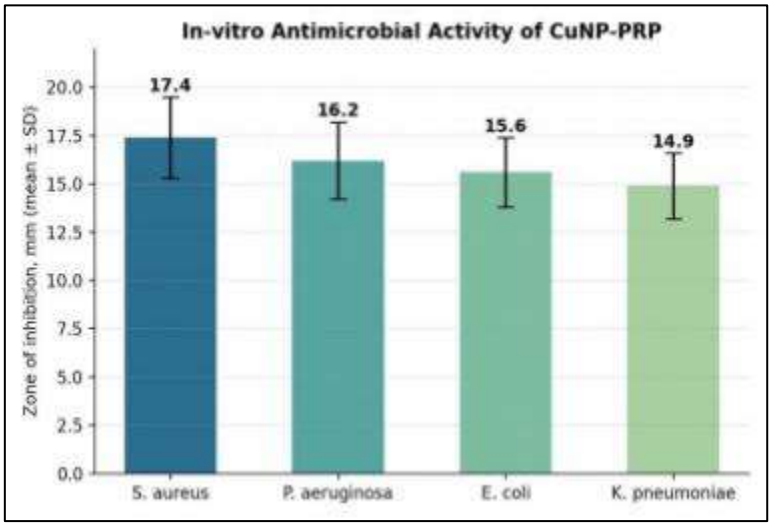


Figure 5. In-**vitro antimicrobial activity ofthe CuNP-PRP formulation against common wound pathogens**

3.4Wound heal ng progress and clinical outcome

Mean wound size decreased progressively from 6.46 ± 2.17 cm² at baseline to 4.8 ± 1.6 cm² at week 2 (25.7% reduction), 3.1 ± 1.4 cm² at week 4 (52.0% reduction), and 0.9 ± 0.31 cm² at week 8 (86.1% reduction from baseline; paired t-test, p<0.001) (Table 6, Table 7, Figure 6). Complete healing was achieved in 60% of patients, with significant improvement in a further 30% and moderate improvement in the remaining 10%; no patient showed a lack of improvement (Table8, Figure 7).

Table 6. Wound healing progress over the 8-week follow-up period.

Time Interval	MeanWoundSize(cm²) SD	Reductionfrom Baseline(%)
Baseline	6.46±2.17	—
Week2	4.8± 1.6	25.7
Week 4	3.1± 1.4	52.0
Week8	0.9±0.31	86.1

Table 7. Comparison of wound size before and after treatment.

Parameter	Mean SD	p value
Baseline woundsize(cm²)	6.46±2.17	
Week8wound size(cm²)	0.9±0.31	<0.001*

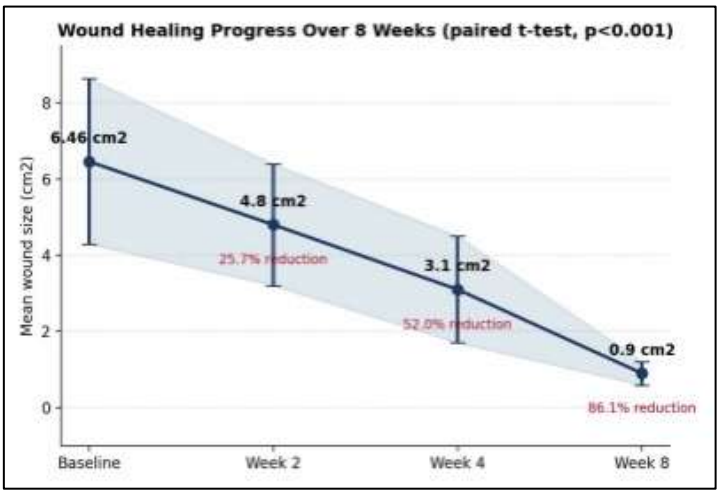


Figure 6. Progressive reduction in mean wound size over the 8-week follow-up period.

Table 8. Overall clinical outcome oftreatment (n=20).

ClinicalOutcome	Number(n)	Percentage(%)
Complete healing	12	60
Significant improvement	6	30
Moderate improvement	2	10

No mprovement	0	0
Total	20	100

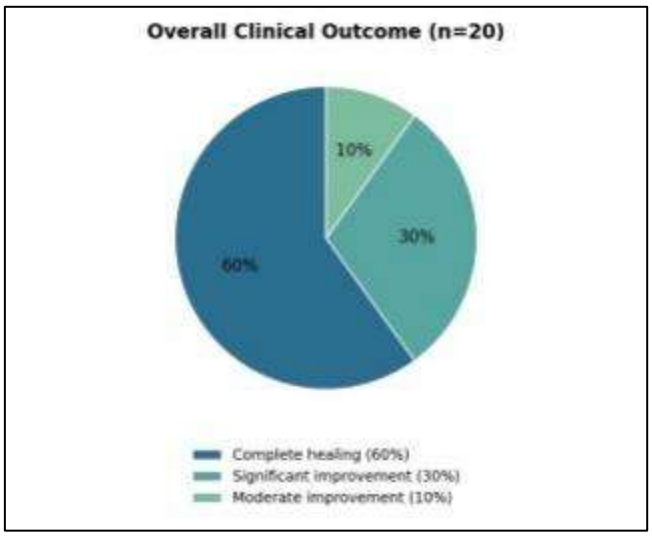


Figure 7. Overall clinical outcome oftreatment.

3.5Wound type and healing outcome

Among diabetic foot ulcers, 50.0% achieved complete healing and 50.0% showed partial healing; among surgical site infections and traumatic wounds, 66.7% achieved complete healing in each group, with the remainder showing partial healing. The chi-square test showed no statistically significant association between wound type and healing outcome (p=0.61), suggesting that the CuNP-PRP formulation performed consistently across the wound aetiologies studied, albeit in small subgroups(Table9, Figure 8).

Table 9. Association between wound type and healing outcome

WoundType	Complete Healing	Partial Healing	Total	p-value
Diabetic foot ulcer	7 (50.0%)	7 (50.0%)	14(70%)	
Surgical site infection	2 (66.7%)	1 (33.3%)	3 (15%)	0.61
Traumatic wound	2 (66.7%)	1 (33.3%)	3 (15%)	

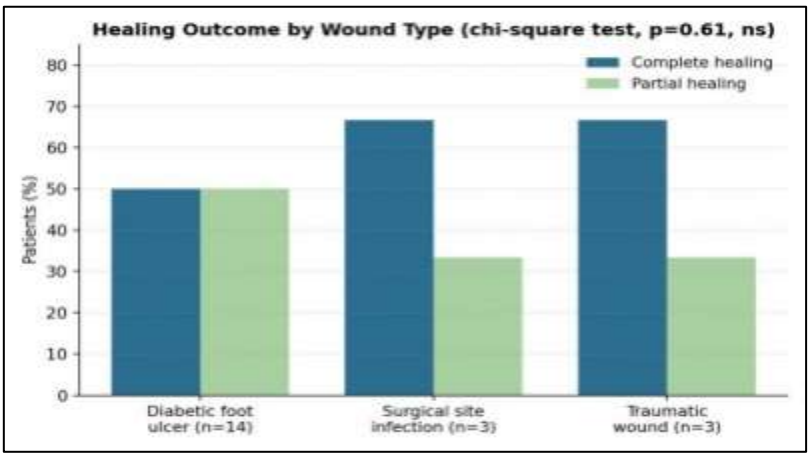


Figure 8. Healing outcome by wound type.

3.6Safety, tolerability, and patient satisfaction

The formulation was well tolerated: 85% ofpatients reported no adverse efects, while 10% experienced mild irritation and 5% experienced local redness, both self-limiting (Table 10, Figure 9). Patient-reported satisfaction was high, with 52.4% highly satisfied and38.1%satisfied;no patient reported dissatisfaction (Table 11, Figure 10).

Table 10.Adverse effects observed following treatment (n=20).

Adverse Effect	Number(n)	Percentage (%)
Noadverseefects	17	85
Mild rritation	2	10

Local redness	1	5
Total	20	100

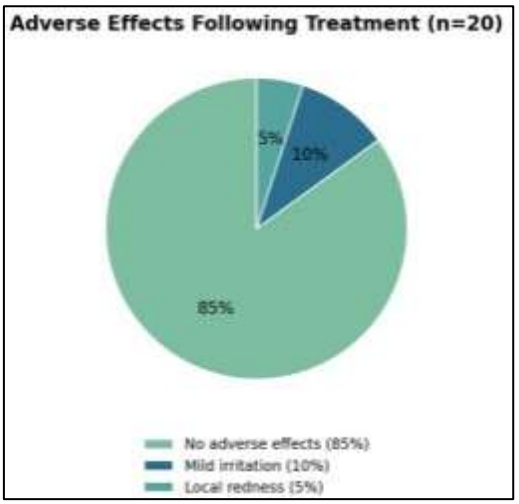


Figure 9. Adverse effects observed following treatment.

Table 11. Overall patient satisfaction following treatment.

Satisfaction Level	Number(n)	Percentage (%)
Highlysatisfied	11	52.4
Satisfied	8	38.1
Neutral	2	9.5
Dissatisfied	0	0
Total	21	100

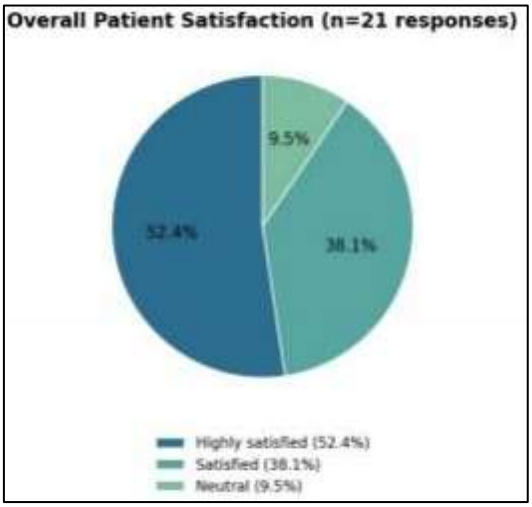


Figure 10. Overall patient satisfaction following treatment

3.7In-vitro cytotoxicity and cell morphology

The cytotoxic potential of copper oxide nanoparticles (CuO NPs) against 3T3-L1 fibroblast cells was assessed by means of the MTT assay following a 24-hour exposure period. Both graphical and quantitative data consistently indicated a concentration-dependent decline in cell viability. At relatively low concentrations ranging from 25 to 100 µL/ml, cell viability was maintained at appreciably high levels (>90%), reflecting favorable biocompatibility within this dosage range. In contrast, a pronounced reduction in cell viability became evident at elevated concentrations, most notably at 200 µL/ml and 250 µL/ml, where a statistically significant decrease was recorded ($p < 0.05$). The table further presents optical density (OD) values, percentage viability, mean ± standard deviation, and statistical significance, confirming that cytotoxicity increases with increasing nanoparticle concentration. Lower concentrations did not show statistically significant toxicity, whereas higher concentrations demonstrated significant effects. Overall, these findings indicate that CuO nanoparticles are biocompatible at lower concentrations but exhibit dose-dependent cytotoxic effects at higher doses, supporting the importance of dose optimization for safe biomedical applications.

24h							
	CuO Np's (µl/ml)						
	Control	25	50	100	150	200	250
O.D	0.826	0.824	0.812	0.809	0.625	0.475	0.353
O.D	0.798	0.792	0.779	0.765	0.732	0.512	0.326
O.D	0.625	0.582	0.579	0.556	0.549	0.492	0.365
%	100	99.758	98.30508475	97.94188862	75.66585956	57.50605327	42.78450363
	100	99.2481203	97.619	95.865	91.72932331	64.160401	40.85213033
	100	93.12	92.64	88.96	87.84	78.72	58.4
Mean	100	97.37532985	96.18804412	94.25551676	85.07839429	66.79548476	47.34554465
SE	0	3.694026949	3.091783393	4.70219005	8.38024859	10.84968358	9.622071187
p-Value		0.161262269	0.05890007	0.061562673	0.059530384	0.028964494	0.022166727

Table 12. Effect of CuO nanoparticles on the viability of3T3-L1 fibroblast cells (MTTassay, 24 h) – source data table.

Cell Morphology

Morphological assessment of 3T3-L1 fibroblast cells was performed using phase contrast microscopy after 24 hours of exposure to CuO nanoparticles. Control cells exhibited normal spindle-shaped morphology with intact cellular structure and confluency. Cells treated with 100 µL/ml of CuO nanoparticles showed mild morphological alterations, including slight reduction in cell density. In contrast, cells treated with 200 µL/ml demonstrated marked morphological changes, including cell shrinkage, rounding, detachment, and reduced confluency, indicating cytotoxic effects at higher concentrations. These observations correlate with the MTT assay results, confirming dose-dependent cytotoxicity of CuO nanoparticles.

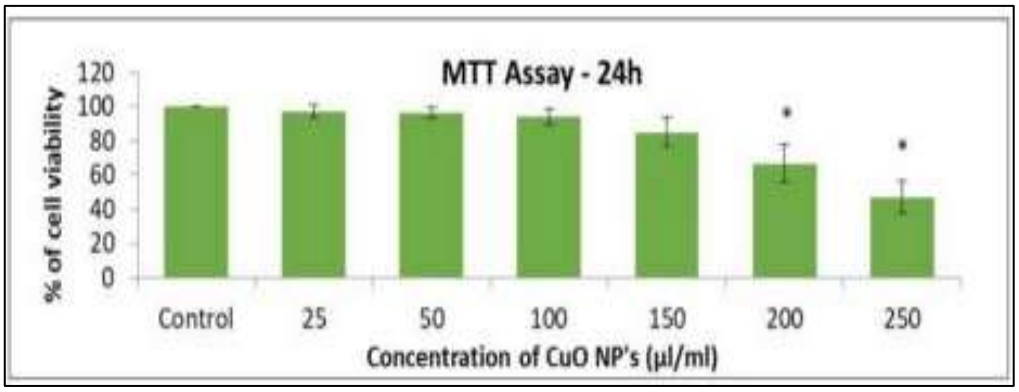


Figure 11. Effect of CuO nanoparticles on cell viability of3T3-L1 fibroblast cells (MTTassay, 24 h).

Phase-contrast microscopy corroborated the MTT findings: control cells showed normal spindle-shaped morphology and confluency; cells exposed to 100µL/mL CuO NPs showed only mild morphological alteration; and cells exposed to 200 µL/mL showed marked shrinkage, rounding, detachment, and reduced confluency, consistent with cytotoxicityathigher doses (Figure 12).

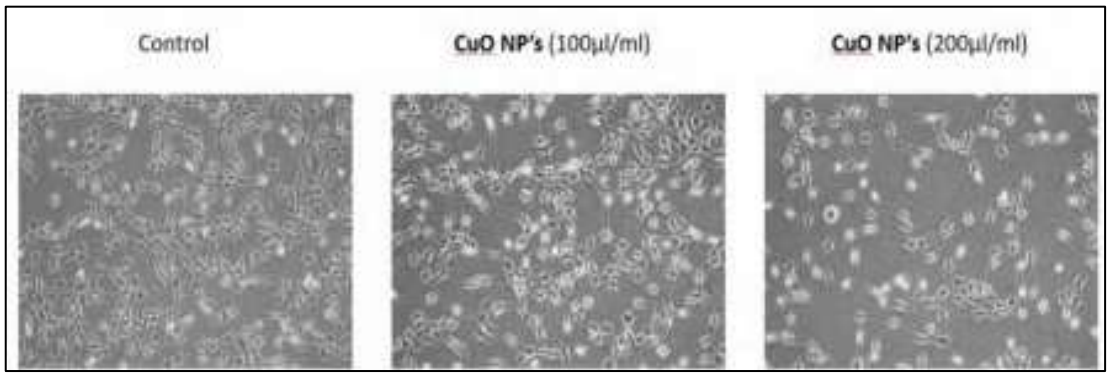
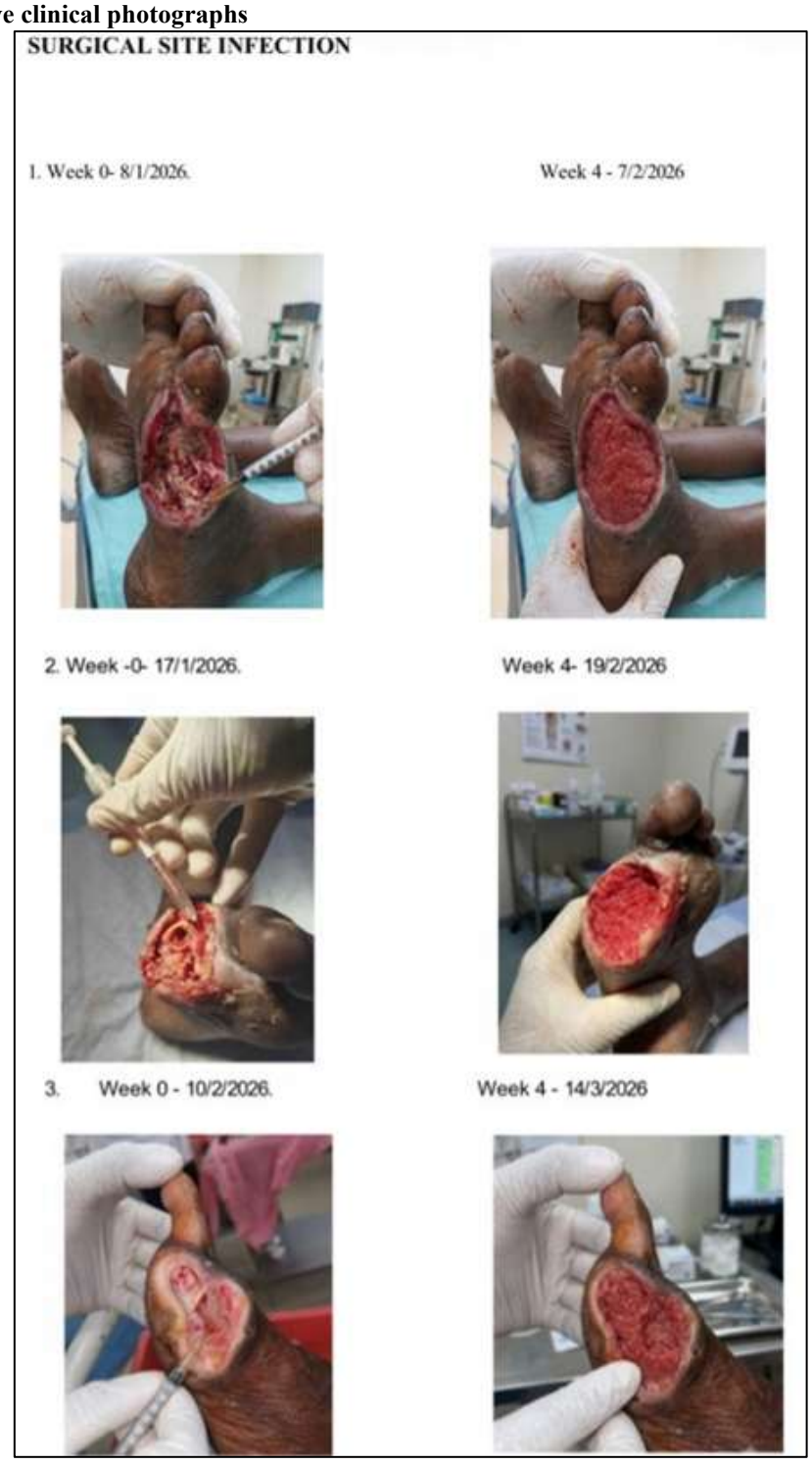


Figure 12. Morphological changes in 3T3-L1 fibroblast cells following 24-hour treatment with CuO nanoparticles (phase- contrast microscopy): control, 100µL/mL, and 200µL/mL (left to right).

3.8 Representative clinical photographs



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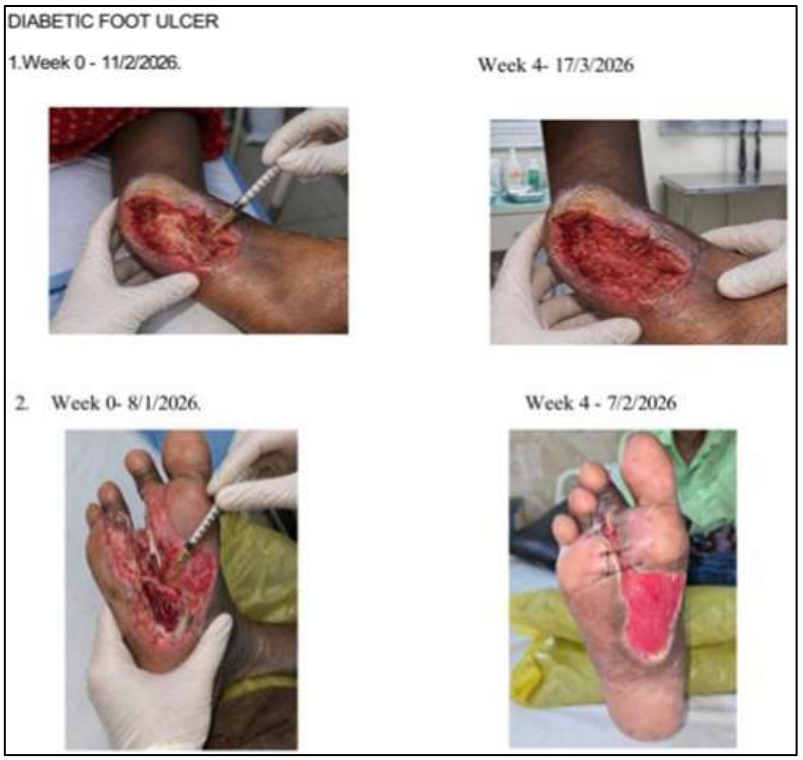

Figure 13. Representative baseline (week 0) and week-4 clinical photographs ofa surgical site infection, a traumatic wound, and a diabetic foot ulcer treated with CuNP-PRP, illustrating progressive granulation and wound-size reduction.

4. DISCUSSION

This prospective study evaluated a novel copper nanoparticle-incorporated PRP nanocomposite designed to combine the regenerative properties of PRP with the antimicrobial and angiogenic effects of copper nanoparticles. The demographic profile observed – predominance of the 46–60-year age group and male preponderance – mirrors previously reported chronic-wound populations, in which advancing age, prolonged diabetes duration, vascular insufficiency, and greater occupational trauma exposure are recognised contributors to delayed healing.21_ 22 Similarly, the predominance of diabetic foot ulcers (70%) in our cohort is consistent with the substantial global burden of diabetic wounds, which affect up to a quarter of people with diabetes over their lifetime.6 The broad-spectrum antimicrobial activity observed, greatest against Staphylococcus aureus, aligns with previous reports that Gram-positive organisms are particularly susceptible to copper-mediated oxidative and membrane-disruptive mechanisms.30 _ 33 Because copper nanoparticles act through several simultaneous mechanisms – membrane disruption, reactive oxygen species generation, and interference with microbial protein and nucleic acid synthesis – the likelihood of resistance development is considered lower than with single-target conventional antibiotics.15 Unlike PRP alone, which acts principally through growth-factor- mediated regeneration, the addition of copper nanoparticles conferred a distinct antimicrobial benefit that would be expected to particularly benefit infected or colonised wounds.

The marked reduction in wound size (86.1% by week 8, $p<0.001$), with early improvement evident by week 2, is consistent with the known ability of PRP-derived growth factors (PDGF, VEGF, TGF-β) to accelerate angiogenesis, fibroblast proliferation, and extracellular matrix remodelling. 9 _ 11 Copper nanoparticles have additionally been shown to promote angiogenesis via the HIF-1α–VEGF axis, offering a plausible mechanistic basis for the synergy observed in this study. 17 37 The absence of a significant association between wound aetiology and healing outcome ($p=0.61$) suggests the formulation may be broadly applicable across wound types, though the small subgroup sizes (n=3 for surgical site infection and traumatic wound) limit the strength of this inference.

Safety and tolerability findings were reassuring, with the large majority of patients experiencing no adverse effects and high patient satisfaction, consistent with the established safety profiles of both PRP and copper-based wound therapies used at appropriate concentrations.1239 The in-vitro cytotoxicity data reinforce the importance of dose selection: while low concentrations (25–100 µL/mL) were well tolerated by fibroblasts, concentrations at or above 200 µL/mL produced significant, dose-dependent toxicity, in keeping with the broader literature on concentration-dependent nanoparticle cytotoxicity.4 2_ 4 4 These findings underscore that the therapeutic window of CuNP-based formulations must be carefully defined to preserve antimicrobial efficacy while avoiding cytotoxic concentrations.

Table 13 places the present findings in the context of previously published work on copper nanoparticles and PRP in wound healing. While individual reports have separately documented the antimicrobial potency of copper nanoparticles and the regenerative efficacy of PRP, direct clinical evaluation of a combined CuNP-PRP nanocomposite, as performed here, remains scarce, supporting the novelty of this work.

Table 13. Comparison ofthe present findings with selected previously reported studies on copper nanoparticles and PRP in wound healing.

Study(year)	Formulation / Model	Key Antimicrobial/Healing Finding	Reference
Sandoval et al. (2022)	Copper nanoparticles, in-vivo/in-vitro wound models (systematic review)	Consistent acceleration of wound closure and antibacterial effect across	[27]
Hakimzadeh& Kosar (2024)	Green-synthesized CuNPs, fibroblast scratch assay	Enhanced fibroblast migrationandwound closureat 16–24 h; anti- inflammatoryiNOSefect	[28]
Meznericset al. (2022)	PRP, meta-analysisofRCTsin chronic wounds	Significant mprovementin wound healingoutcomes with PRPvs. standard care	[24]
Azametal. (2024)	PRP, diabetic foot ulcer patients	Improved healng ratesand reduced ulcer sizewith autologousPRP	[23]
Salvo&Sandoval (2022)	Copper nanoparticles, chronicwound review	Angiogenicand antimicrobial synergy proposed forcombned nanoparticle-regenerative therapy	[20]
Present study(2026)	CuNP-PRPnanocomposite, mixed acute/chronic wounds (n=20)	Zoneof inhibition upto 17.4 mm(S. aureus); 86.1% wound size reduction by week8; 60%complete healing	—

5. LIMITATIONS

- Small sample size (n=20)analysed from a single centre, limiting statistical power and generalisability.
- Absence of a control or comparator arm(e.g., standard wound care or PRP alone), precluding direct comparative efficacy claims.
- Relatively short follow-up (8weeks), insufficient to assess long-term healing durability or recurrence.
- Limited molecular/histopathological characterisation ofthe healing mechanism in clinical specimens.
- Potential selection bias from consecutive convenience sampling ata single institution.

6. CONCLUSION

Copper nanoparticle-incorporated platelet-rich plasma demonstrated significant broad-spectrum antimicrobial activity, accelerated wound closure, a high rate of complete healing, and good biocompatibility and tolerability in this prospective study of acute and chronic wounds. In-vitro data confirm a favourable safety margin at low- to-moderate CuO nanoparticle concentrations, with dose-dependent cytotoxicity emerging only at higher concentrations, underscoring the need for careful dose optimisation. CuNP-PRP represents a promising, potentially cost-effective adjunct for wound management, particularly relevant to resource-limited settings; larger, randomised, controlled studies with extended follow-up are needed to confirm these findings and establish long-term efficacy and safety.

RECOMMENDATIONS FOR FUTURE RESEARCH

- Conduct adequately powered randomised controlledtrials with a standard-care or PRP-only comparator arm.
- Extend follow-up to evaluate durability of healing and recurrence rates.
- Explore alternative delivery formats(gel, injectable, impregnated dressing) and dose optimisation.
- Undertake molecular and histopathological studies to clarify the mechanism ofthe CuNP-PRP synergy.
- Evaluate effectiveness specifically in high-risk subgroups such as patients with diabetes.

ETHICS STATEMENT

The study was approved by the Institutional Ethics Committee, Saveetha Medical College and Hospital (IEC Ref. No. 024/09/2025/IEC/SMCH) and prospectively registered with the Clinical Trials Registry – India (CTRI/2026/03/105841). Written, bilingual informed consent was obtained from Allparticipants.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest relevant to this manuscript.

FUNDING

No external funding was received for this study.

AUTHOR CONTRIBUTIONS

Varsha S: study concept, data acquisition, laboratory and clinical work, analysis, and manuscript drafting. Dr. Vivarsha: study supervision, critical revision, and final approval. Both authors read and approved the final manuscript.

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