ORIGINAL ARTICLE

Evaluation of Copper Nanoparticle Nanosolution as an Adjunctive Treatment for Chronic Gingivitis in Cats: A Clinical and Histological Study

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Abstract

Introduction: Chronic gingivitis is a prevalent periodontal inflammatory disorder that can progress to a destructive disease and shows limited responsiveness to conventional treatment. Copper nanoparticles exhibit antimicrobial activity and may modulate inflammation and support tissue repair; however, their therapeutic value needs to be validated. This study evaluated the clinical and morphofunctional effectiveness of local 0.1% copper nanosolution therapy for chronic gingivitis in 40 mixed-breed cats aged 3–5 years. **Methods:** Following ethical approval (Protocol No. 231, dated July 17, 2019), all animals underwent standardized oral examination, photographic documentation, and ultrasonic scaling. Each animal then received 2 mL of 0.1% copper nanosolution injected submucosally into the upper and lower jaws, with repeated administrations over a 21-day observation period. Clinical outcomes were assessed on days 1, 7, 14, and 21, and gingival biopsies were collected on days 1 and 21 for hematoxylin and eosin histology. **Results:** By day 21 (after three administrations), most cats showed marked clinical improvement: gingival bleeding ceased in 35/40 (87.5%), swelling decreased in 33/40 (82.5%), halitosis resolved in 31/40 (77.5%) and improved in the remainder, and normal feeding behavior returned in 36/40 (90.0%); no complications or deaths were observed. The periodontal pocket depth decreased from 3.75 ± 0.28 mm to 1.35 ± 0.15 mm (64.0% reduction), and the histopathological inflammation scores declined from 3.6 ± 0.5 to 1.0 ± 0.3 (72.2% reduction). Histological analysis corroborated reduced inflammatory infiltration (by 40–50%) and enhanced reparative remodeling with fibroblast proliferation, collagen deposition, angiogenesis, and improved epithelial integrity. **Conclusion:** These findings support copper nanosolution injections as a promising adjunctive anti-inflammatory and regenerative approach for feline chronic gingivitis, while underscoring the need for larger randomized controlled trials with controls, longer follow-up, and molecular/microbiological endpoints to confirm their efficacy, durability, and safety.

Key words: Antimicrobial activity, chronic gingivitis, copper nanoparticles, periodontal tissue repair, wound healing

INTRODUCTION

Chronic gingivitis is one of the most prevalent inflammatory conditions affecting the periodontal tissues. It is characterized by prolonged duration, disrupted microcirculation, destructive soft tissue changes, and a high likelihood of progression to more severe periodontal diseases. The limited success of conventional treatments, including

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professional oral hygiene and antiseptics, has driven the search for novel therapies with anti-inflammatory and regenerative benefits. Recent advances in nanomedicine have highlighted the use of metal nanoparticles in dental applications. Copper nanosolutions have attracted attention for their antimicrobial properties, ability to inhibit pathogenic oral microflora, reduce inflammation, and promote periodontal tissue repair.[1] Metal nanoparticles and their oxides are emerging antimicrobial agents. At the nanoscale, copper and gold nanoparticles exhibit activity against Gram-positive and Gram-negative bacteria, including fungal pathogens. Given the potential of copper and its oxide nanoparticles in antimicrobial treatments, this study reviews the literature on their biological properties, mechanisms of action, and factors influencing their efficacy, including the polymer matrix.[2]

Copper nanoparticles exhibit biological activity, including bacteriostatic and bactericidal effects. In animals, nanoparticle copper preparations have prolonged effects and lower toxicity than salt-based compounds. In the body, they activate mechanisms that regulate trace element balance and antioxidant enzyme activity. Metal nanostructures are considered promising antibacterial agents.[3] Experimental *in vitro* and *in vivo* studies have yielded promising results. Aqueous solutions of copper and gold nanoparticles exhibit antibacterial activity, particularly against *Staphylococcus aureus*. However, their effect on gram-negative bacteria, such as *Escherichia coli*, is less pronounced because of the structural characteristics of the cell walls of these microorganisms.[4]

All tested copper nanoparticle solutions exhibited significant antimicrobial effects against *S. aureus* and *E. coli*. Aqueous solutions of silver and copper nanoparticles were more potent than their dialyzed counterparts, showing higher efficacy against *S. aureus* than against *E. coli*, likely due to gram-negative cell wall structures. These findings suggest that metal nanoparticle solutions effectively combat multidrug-resistant microorganisms.[5] Cu^{+} ions exert stronger bactericidal effects than Cu^{2+} ions by penetrating membranes and deactivating iron-sulfur clusters. The primary antimicrobial mechanism, "contact destruction," involves direct interactions between copper surfaces or nanoparticles and cell membranes.[6] Providing evidence for laser nanotechnology is a key clinical objective, as laser medicine has shown high efficacy in experimental studies. Analysis determined that 1 mg/ml copper nanoparticles possess the highest bactericidal activity.[7] The rapid emergence of antibiotic resistance underscores the need for alternative agents. The effectiveness of metal nanoparticles stems from their small size and surface area, which facilitates close contact with membranes.[8] Several authors have investigated the activity of copper nanoparticles on museum strains.[9]

The findings from these studies formed the foundation for the US Environmental Protection Agency's approval of copper nanoparticles as an antimicrobial agent to tackle pathogenic microorganisms.[10] Given the significance of trauma-related issues, ongoing research is being conducted to develop new wound-healing medications. Wound healing is a complex biological process that requires the interaction of trace elements, antioxidant systems, matrix metalloproteinases, and other biologically active substances. Copper deficiency hinders reparative processes. Using a copper nanosolution to treat chronic gingivitis seems promising, as it improves treatment efficacy, accelerates tissue regeneration, and reduces the risk of inflammation recurrence. Investigating its therapeutic potential holds scientific and practical value for the advancement of periodontal disease treatment methods.[11]

It is now recognized that metal nanoparticles can provoke a biological response distinct from traditional ionic forms of elements upon entering the body. Research on nanoparticles in biosystems has revealed their unique characteristics. D-element nanoparticles are 7–50 times less toxic than metal ions. Their ability to serve as reservoirs of microelements in the body allows for prolonged biological effects. In biologically acceptable doses, they stimulate metabolic processes and exhibit multifunctional activity. This provides a scientific foundation for the development of a new class of nanoparticle-based medications.[12] Annexin test results indicated that incubating cell cultures with copper nanoparticles led to increased apoptosis and necrosis compared to control samples.[13] These findings underscore the significant potential of nanomaterials as active components in pharmaceuticals and drug delivery systems, contributing to the advancement of nanomedicine as a novel direction in medical science for both research and clinical practice.

This study aimed to evaluate the effectiveness of using a copper nanosolution to treat chronic gingivitis in 40 mongrel cats aged 3–5 years.

METHODS

A total of 40 animals were included in the study. The Ethics Committee of the Scientific and Production Association "Preventive Medicine" under the Ministry of Health of the Kyrgyz Republic reviewed and approved this study (Protocol No. 231, dated July 17, 2019). Animal inclusion adhered to the principles of humane treatment and biosafety standards. During the experiment, a copper nanosolution was injected into the submucosal areas of the upper and lower jaws. Before this, all cats underwent oral hygiene. Animals with chronic gingivitis were selected, many of whom had oral mucosal disease and weight loss due to impaired chewing. Solid food often caused bleeding gums or refusal to eat, and some animals preferred soft food. For 6 months, the owners administered prednisolone at the recommended dosage for oral mucosa inflammation, but prolonged use yielded no positive clinical outcomes: Gum inflammation persisted, and the condition did not improve. This underscores the limited efficacy of conventional therapies and the need to investigate alternative treatments.

Oral examination revealed brown cervical plaques and molar tartar. To objectively track periodontal tissue changes, a photographic protocol was used to document the initial state before ultrasonic dental cleaning and immediately after the procedure for comparative analysis. The lighting, angle, and distance were constant, providing a measure of treatment effectiveness. Dental plaque removal in all animals was performed using an ultrasonic scaler at medium power. Each animal received a 2 mL injection of a 0.1% copper nanosolution into the submucosal region of the upper and lower jaws. The study algorithm included intramuscular medetomidine based on body weight, followed by Zoletil administration 15 min later. Before cleaning, a gum tissue sample was excised for histological examination and placed in 10% neutral-buffered formalin. The tissue was then disinfected with 0.5% hydrogen peroxide. A sterile scalpel and biopsy forceps were used to remove the gum portion, after which gauze swabs soaked in 3% hydrogen peroxide were applied. Paraffin sections (5–6 µm thick) were stained with hematoxylin and eosin using histological methods. Samples were collected on days 1 and 21.

On the 21st day following three doses of the copper nanosolution, clinical examination of the animals showed improvement, as evidenced by decreased gingival tissue swelling, no bleeding upon mechanical irritation, and elimination of bad breath. These findings suggest reduced inflammatory activity and a gradual return of the gingival mucosa to normal conditions. Clinical assessments were performed on days 1, 7, 14, and 21 to monitor recovery. After the initial injection of the copper nanosolution, no significant improvements were noted, highlighting the need for repeated doses to achieve the desired benefits. For histological evaluation, samples were collected at 2 time points: the first and 21st days of the study, allowing comparison of tissue conditions with their post-treatment state and assessment of reparative processes and connective tissue remodeling.

RESULTS

Forty mixed-breed cats (3–5 years old) with chronic gingivitis underwent professional ultrasonic scaling and submucosal injections of 0.1% copper nanosolution. The application of a copper nanosolution for the treatment of chronic gingivitis in cats showed significant clinical and morphofunctional effectiveness. The study findings indicated that 85–90% of the cats experienced complete cessation of gum bleeding, whereas 80–85% experienced a marked decrease in mucosal swelling. No treatment-related complications or death were observed.

Initially, all cats exhibited chronic gingivitis, including redness, swelling, bleeding, plaque, halitosis, and discomfort while chewing [Table 1]. Many patients preferred soft foods because of pain.

Clinical improvements were observed with repeated nanosolution administration. Minimal changes were observed after the first injection; however, significant therapeutic effects emerged after the second and third sessions. By day 21, most cats showed a substantial reduction in inflammation.

Quantitative evaluation showed the restoration of periodontal health. The mean pocket depth decreased from 3.75 ± 0.28 mm to 1.35 ± 0.15 mm (64.0% reduction). The severity of gingival inflammation, assessed using a histopathological scale, decreased from 3.6 ± 0.5 to 1.0 ± 0.3 points by day 21 (72.2% reduction) [Table 2].

Pre-treatment microscopic examination revealed severe inflammation, including stromal swelling, vascular congestion, bleeding, epithelial degeneration, and lymphoplasmacytic infiltration [Table 3]. Post-treatment, inflammatory infiltration decreased by 40–50%. Connective tissue remodeling, characterized by fibroblast proliferation, collagen deposition, and active angiogenesis, occurred. These findings, along with the restored epithelial integrity, suggest activated reparative and regenerative processes.

Gingival bleeding stopped in 35 (87.5 %) cats, and swelling decreased in 33 (82.5%) cats [Table 4]. Halitosis resolved in 31 (77.5%) patients and improved in the others. Normal eating behavior returned in 36 cats (90.0%), indicating reduced discomfort. By the end of the study, no purulent discharge or abnormal tooth mobility remained, indicating a high response rate.

Table 1: Clinical response to copper nanosolution therapy

Parameters	Baseline (%)	Post-treatment (%)	Improvement
Gingival bleeding	40 (100)	5 (12.5)	87.5
Gingival edema	40 (100)	7 (17.5)	82.5
Halitosis	40 (100)	9 (22.5)	77.5
Reduced appetite	40 (100)	4 (10.0)	90.0
Pain during chewing	40 ((100)	6 (15.0)	85.0
Purulent discharge	Present	0	Complete resolution

Data presented as *n* (%), *n*=number of patients, %=percentage of patients

Table 2: Quantitative periodontal outcomes

Variables	Baseline	Day 21	Change
Periodontal pocket depth (mm)	3.75±0.28	1.35±0.15	−64.0
Inflammatory score (0–4)	3.6±0.5	1.0±0.3	−72.2
Bleeding tendency score	3.4±0.4	0.5±0.2	−85.3
Gingival edema score	3.3±0.5	0.7±0.3	−78.8

Data presented as %=percentage of patients, mean±standard deviation (M±m)

Nevertheless, to comprehensively assess the efficacy and safety of this treatment, larger randomized trials with more extensive animal samples, control groups, and long-term outcome evaluations are required. Overall, the data suggest that copper nanosolutions hold promise in veterinary dentistry and could serve as a foundation for developing innovative treatments for inflammatory periodontal disease in animals.

Representative clinical case

This study presents a clinical case of chronic gingivitis in a cat treated with a copper nanosolution. A 1.5-year-old cat weighing 1.6 kg was brought to the emergency department. The owner reported difficulty in eating, refusal of solid food, and reduced appetite.

Initial examination revealed hyperemic, swollen, and friable gums that bled on palpation. An inflammatory ridge was present along the dental line, the tissues were painful, and an unpleasant odor emanated from the mouth. The cat was weakened. The gums exhibited inflammatory changes typical of chronic gingivitis, with friability, bleeding on contact, and color ranging from bright red to cyanotic. The cat experienced discomfort while eating and had a reduced appetite. These findings indicate long-standing chronic inflammation requiring treatment and regular check-ups. The preliminary diagnosis was chronic gingivitis.

The treatment plan began with thorough ultrasonic dental cleaning to remove soft and hard plaque and prepare for the injection therapy. A copper nanosolution (0.1% concentration) was injected into the transitional fold of the upper and lower jaws once every 7 days for a month (four sessions). After the second session, the swelling, hyperemia of the gingival margin, and pain decreased. By the third session, the bleeding on palpation had stopped, the appetite had improved, and the cat began eating soft food. By the end of treatment, the gingival mucosa was pale pink, the tissue structure had thickened, and the inflammatory ridge along the tooth line had diminished. The bad breath decreased, and the condition improved. A gum biopsy was performed before and after treatment, and the samples were fixed under standard conditions for histological examination of structural changes in the gingival tissue.

Local copper nanosolution injections have shown significant anti-inflammatory and regenerative effects in chronic gingivitis in experimental animals. This method reduced pain, normalized the gingival mucosa, and restored chewing function. Ultrasonic professional dental cleaning is currently performed twice a year to maintain periodontal tissue, prevent plaque accumulation, reduce oral mucosal inflammatory diseases, and support the prevention of chronic dental diseases.

The gingival histology of an animal on the 1st day before copper nanosolution administration was characterized by hemorrhage, severe edema, and cytoplasmic vacuolation [Figure 1]. The superficial mucosal areas partially retained the stratified squamous epithelium. Layers of coarse fibrous connective tissue with foci of lymphoid infiltration were visible in the underlying layers, and the gingival tissue was saturated with blood.

Table 3: Histopathological assessment of the gingival tissue

Histological features	Baseline	Day 21
Stromal edema	Severe	Mild
Vascular congestion	Marked	Minimal
Hemorrhage	Frequent	Rare
Lymphoplasmacytic infiltration	Dense	Decreased by 40–50%
Epithelial degeneration	Pronounced	Minimal
Fibroblast activity	Low	High
Collagen organization	Disorganized	Well-organized
Neovascularization	Absent/Minimal	Prominent
Tissue regeneration	Absent	Active

Table 4: Overall treatment success

Endpoints	Responders (%)
Bleeding cessation	35/40 (87.5)
Edema reduction	33/40 (82.5)
Appetite normalization	36/40 (90.0)
Pain reduction	34/40 (85.0)
Histological improvement	38/40 (95.0)
Overall clinical success	35/40 (87.5)

Data presented as *n* (%), *n*=number of patients (Responders), %=percentage of patients (response rate)

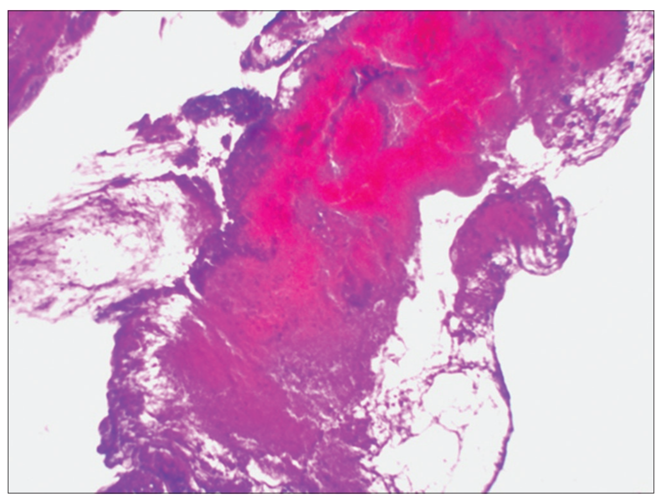

Figure 1: Hematoxylin and eosin staining demonstrating the gingival histology of an experimental animal before treatment

The gingival histology of an animal 21 days after the application of a copper nanosolution demonstrated clusters of lymphoid tissue interspersed with thickened, irregularly oriented collagen fibers, indicating chronic inflammation [Figure 2]. These areas showed an increase in lymphocytes

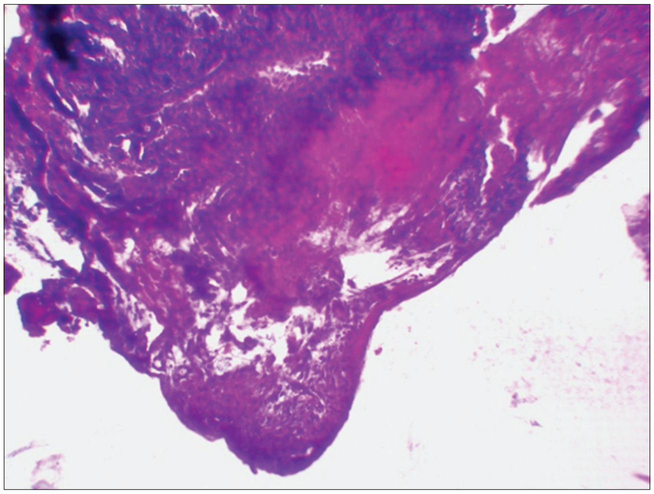

Figure 2: Hematoxylin and eosin staining demonstrating the gingival histology of an experimental animal after treatment

and plasma cells. The gingival layer was partially lined with stratified squamous non-keratinizing epithelium, with thinning and disruption of the integumentary layer. Epithelial cells showed dystrophic changes, including cytoplasmic vacuolization and reduced nuclear size. The underlying connective tissue showed microvascular dilation and moderate interstitial edema. These changes indicate sluggish inflammation, connective tissue restructuring, partial epithelial atrophy, adaptive reactions to prolonged inflammatory irritation, and decreased mucous membrane barrier function.

DISCUSSION

This study has revealed that local administration of a 0.1% copper nanosolution leads to clinical and histopathological improvements in cats with chronic gingivitis. Post-treatment, most animals showed cessation of gingival bleeding, decreased edema and halitosis, regained appetite, and improved periodontal tissue structures. Histological examination validated decreased inflammatory infiltration and increased fibroblast activity, collagen formation, and angiogenesis. These results indicate that copper nanosolutions have anti-inflammatory and regenerative effects on periodontal tissues.

Chronic gingivitis involves inflammatory infiltration, epithelial barrier damage, vascular congestion, and the destruction of connective tissue. If left untreated, gingivitis can progress to periodontitis, causing irreversible harm. Although professional cleaning is primary, recurrence is frequent due to bacterial biofilm recolonization. Thus, there is interest in adjunctive therapies that manage microbial growth and encourage regeneration.[2,14]

Clinical improvements may be linked to the antimicrobial properties of copper nanoparticles. Copper-based nanomaterials exhibit broad-spectrum antibacterial effects by disrupting bacterial membranes, producing reactive oxygen species, denaturing proteins, and damaging nucleic acids. Unlike antibiotics, these mechanisms lower the risk of microbial resistance.[6,15] Previous studies have shown that copper nanoparticles are effective against Gram-positive and Gram-negative oral pathogens.[16,17] The reduction in inflammation and halitosis is consistent with these characteristics.

A key finding was the significant decrease in periodontal pocket depth and inflammatory score. These improvements likely result from bacterial suppression and modulation of the host inflammatory response. Copper ions are involved in biological processes such as cytokine regulation, extracellular matrix remodeling, angiogenesis, and fibroblast proliferation.[18,19] Copper is a crucial cofactor for lysyl oxidase and is necessary for collagen cross-linking. The improved collagen organization may be attributed to the role of copper in extracellular matrix synthesis and stabilization.[20]

Histological findings provide evidence of the regenerative potential of copper nanosolutions. Before treatment, the tissues showed severe edema, bleeding, epithelial degeneration, and infiltration. By day 21, inflammatory infiltrates decreased, whereas fibroblast proliferation and blood vessel formation increased. Similar findings have been reported in wound-healing studies, where copper nanoparticles accelerated granulation, stimulated angiogenesis, and enhanced tissue remodeling.[12] Sandoval *et al*. concluded that copper nanoparticles improve wound closure and tissue repair by activating angiogenic and antioxidant pathways.[12]

A significant finding was the swift recovery of feeding habits in approximately 90% of the treated animals. Gum inflammation often impairs the nutrition and well-being of pets. Improved appetite and chewing indicated that copper nanosolution therapy reduced inflammatory pain and restored oral function. Similar outcomes after veterinary periodontal treatment highlight the importance of controlling oral inflammation in animal health.[21]

Recent advances in nanodentistry underscore the importance of metallic nanoparticles in preventing and treating oral conditions. Copper nanoparticles offer several advantages over other nanomaterials, including lower production costs, strong antimicrobial properties, and beneficial interactions with host tissues.[2,3] They exhibited lower toxicity than ionic copper compounds at biologically safe levels, supporting their clinical potential.[22]

However, this study has several limitations. The study lacked an untreated control group and comparison with standard treatments, limiting the attribution of benefits solely to copper nanosolution therapy. The sample size was small and from a single experimental context. Inflammatory markers such as interleukin-1β, tumor necrosis factor-α, and C-reactive protein were not measured, limiting the understanding of tissue-recovery mechanisms. Long-term follow-up was absent, leaving the effect durability and recurrence rates uncertain.

CONCLUSION

The findings of this study indicate that copper nanosolution therapy is linked to reduced gum inflammation, improved periodontal health, and activation of tissue repair. The observed antimicrobial, anti-inflammatory, and regenerative effects support the potential application of copper nanosolutions as an innovative supplementary treatment for chronic gingivitis in veterinary patients.

Future research should include randomized controlled veterinary trials with larger sample sizes, longer observation periods, microbiological studies, and molecular evaluations of inflammatory and regenerative pathways. Exploring copper nanosolutions alongside conventional periodontal treatments may clarify their role in comprehensive care. Comparative studies of other nanomaterials, such as silver or zinc oxide nanoparticles, would help identify the most effective nanotherapeutic approach for veterinary dentistry.

INFORMED CONSENT STATEMENT

Not applicable.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

REFERENCES

1. Litvinenko AA, Kulikova AA, Khabadze ZS, Bakaev YA, Fedotova NN, Karnaeva AS, *et al*. Application of antiseptic composition based on polyaminopropyl biguanide in the chronic catarrhal gingivitis treatment. Endodontics Today 2022;20:197-200.
2. Ma X, Zhou S, Xu X, Du Q. Copper-containing nanoparticles: Mechanism of antimicrobial effect and application in dentistry-a narrative review. Front Surg 2022;9:905892.
3. Amini SM. Preparation of antimicrobial metallic nanoparticles with bioactive compounds. Mater Sci Eng C Mater Biol Appl 2019;103:109809.
4. Belokobylov AA, Batpenov ND, Balgazarov SS, Serikbayev VD, Krikliviy AA, Plotnikov SV, *et al*. Copper-coated spacer for total femoral replacement in recurrent periprosthetic joint infection: A case report. Traumatol Orthop Russia 2021;27:175-82.
5. Swolana D, Wojtyczka RD. Activity of Silver Nanoparticles against *Staphylococcus* spp. Int J Mol Sci 2022;23:4298.
6. Mitra D, Kang ET, Neoh KG. Antimicrobial copper-based materials and coatings: Potential multifaceted biomedical applications. ACS Appl Mater Interfaces 2020;12:21159-82.
7. Fekrazad R, Naghdi N, Nokhbatolfoghahaei H, Bagheri H. The combination of laser therapy and metal nanoparticles in cancer treatment originated from epithelial tissues: A literature review. J Lasers Med Sci 2016;7:62-75.
8. Morones JR, Elechiguerra JL, Camacho A, Holt K, Kouri JB, Ramírez JT, *et al*. The bactericidal effect of silver nanoparticles. Nanotechnology 2005;16: 2346-53.
9. Stanila A, Braicu C, Stanila S, Pop RM. Antibacterial activity of copper and cobalt amino acids complexes. Not Bot Horti Agrobo 2011;39:124-9.
10. Theivasanthi T, Alagar M. Nano sized copper particles by electrolytic synthesis and Characterizations. Int J Phys Sci 2011;6:3662-71.
11. Zapata D, Higgs J, Wittholt H, Chittimalli K, Brooks AE, Mulinti P. Nanotechnology in the diagnosis and treatment of osteomyelitis. Pharmaceutics 2022;14:1563.
12. Sandoval C, Ríos G, Sepúlveda N, Salvo J, Souza-Mello V, Farías J. Effectiveness of copper nanoparticles in wound healing process using *in vivo* and *in vitro* studies: A systematic review. Pharmaceutics 2022;14:1838.
13. Shafagh M, Rahmani F, Delirezh N. CuO nanoparticles induce cytotoxicity and apoptosis in human K562 cancer cell line via mitochondrial pathway, through reactive oxygen species and P53. Iran J Basic Med Sci 2015;18:993-1000.
14. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. Nat Rev Dis Primers 2017;3:17038.
15. Vincent M, Duval RE, Hartemann P, Engels-Deutsch M. Contact killing and antimicrobial properties of copper. J Appl Microbiol 2018;124:1032-46.
16. Ren G, Hu D, Cheng EW, Vargas-Reus MA, Reip P, Allaker RP. Characterisation of copper oxide nanoparticles for antimicrobial applications. Int J Antimicrob Agents 2009;33:587-90.
17. Besinis A, De Peralta T, Handy RD. Inhibition of biofilm formation and antibacterial properties of a silver nano-coating on human dentine. Nanotoxicology 2014;8:745-54.
18. Sen CK, Khanna S, Venojarvi M, Trikha P, Ellison EC, Hunt TK, *et al.* Copper-induced vascular endothelial growth factor expression and wound healing. Am J

Physiol Heart Circ Physiol 2002;282:H1821-7.
19. Borkow G, Gabbay J. Copper as a biocidal tool. Curr Med Chem 2005;12:2163-75.
20. Rucker RB, Kosonen T, Clegg MS, Mitchell AE, Rucker BR, Uriu-Hare JY, *et al.* Copper, lysyl oxidase, and extracellular matrix protein cross-linking. Am J Clin Nutr 1998;67:996-1002S.
21. Niemiec BA. Periodontal disease. Top Companion Anim Med 2008;23:72-80.
22. Chatterjee AK, Chakraborty R, Basu T. Mechanism of antibacterial activity of copper nanoparticles. Nanotechnology 2014;25:135101.

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