The Effect of Chitosan-Silver Nanoparticles (Chi-AgNPs) Synthesized Using *Clinacanthus nutans* Extract on the Viability of MC3T3-E1 Preosteoblast Cells In Vitro

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ABSTRACT

Background: *Chi-AgNPs (chitosan–silver nanoparticles) are antibacterial biomaterials with good biocompatibility potential, but their toxicity to osteoblastic cells still needs to be studied. The objective of this study is to analyze the effect of Chi-AgNPs synthesized using Clinacanthus nutans extract on the viability of MC3T3-E1 preosteoblast cells at several concentrations to determine the safe concentration limit for their use.*

Method: *This laboratory experimental study used MC3T3-E1 cells exposed to Chi-AgNPs at concentrations of 12.5 µg/mL, 25 µg/mL, and 50 µg/mL, with a control group as a comparison. Cell viability was measured using the WST assay after 24 hours of incubation, then analyzed statistically using the ANOVA test to see the differences between groups.*

Result: *The results showed that a concentration of 12.5 µg/mL increased the average viability value by 30.8%, while a concentration of 25 µg/mL did not show a significant difference in cell viability compared to the control. Conversely, a concentration of 50 µg/mL caused a significant decrease in viability ($p < 0.05$), indicating toxicity related to the release of Ag^+ ions and increased oxidative stress due to the small size of the nanoparticles (20 ± 3.93 nm).*

Conclusion: *Chi-AgNPs are safe and biocompatible with MC3T3-E1 cells at concentrations below 25 µg/mL*

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INTRODUCTION

The advancement of biomaterials has become an important focus in modern healthcare research, particularly in dentistry and bone tissue engineering. The development of materials that combine antimicrobial properties with biocompatibility is essential to prevent infection while supporting tissue regeneration. Among many biomaterials, chitosan stands out due to its biocompatibility, biodegradability, and minimal toxicity, while silver nanoparticles are widely recognized for their strong and broad-spectrum antibacterial properties.[1,2] Silver nanoparticles are combined with chitosan to provide broad-spectrum antibacterial protection. This combination is expected to address the critical problem of healthcare-associated infections, 60%–70% of which are associated with medical implants.[3] The combination of chitosan and silver nanoparticles in the form of Chitosan–Silver Nanoparticles (Chi-AgNPs) is therefore considered a promising strategy for biomedical applications. Research indicates that chitosan based scaffolds create an osteogenic like microenvironment that facilitates preosteoblast differentiation, accelerates biomineralization, and promotes the generation of a mineralized bone matrix. Furthermore, silver nanoparticles within these composites can enhance osteoblast activity and improve the mechanical robustness of repaired bone, thereby expediting the overall regeneration process.[4,5] Despite their potential advantages, the incorporation of silver nanoparticles into biomaterials raises concerns regarding biological safety. Silver nanoparticles are known to exhibit cytotoxic effects depending on their size, concentration, and exposure duration. In bone-related applications, this issue becomes critical because materials used in the oral and maxillofacial region often interact directly with bone-forming cells.[5,6] Consequently, it is necessary to carefully evaluate the biological response of bone-related cells to Chi-AgNPs before considering their further development or clinical application. Preosteoblast MC3T3-E1 cells are often used as an in vitro model to study cellular responses related to bone formation and osteogenic activity. These cells provide a reliable system for evaluating the biocompatibility and cytotoxic potential of biomaterials.[7] One of the most important parameters in such evaluations is cell viability, as it reflects the ability of cells to survive and maintain metabolic activity when exposed to a specific material. Assessing cell viability is therefore a fundamental step in determining whether a material is safe or potentially harmful to bone cells.[8]

Although several studies have reported the antibacterial effectiveness of Chi-AgNPs, data regarding their effects on preosteoblast cell viability remain limited and inconsistent. Differences in nanoparticle size, synthesis methods, and concentration ranges have resulted in varying biological outcomes.[9] In particular, there is insufficient clarity regarding the concentration thresholds at which Chi-AgNPs remain biocompatible or begin to exhibit cytotoxic effects on preosteoblast cells. This lack of clear evidence represents a significant research gap and may hinder the safe application of Chi-AgNPs in bone-related biomedical fields. Based on these considerations, the main problem addressed in this study is the uncertainty regarding the effect of Chitosan–Silver Nanoparticles on the viability of preosteoblast *MC3T3-E1* cells under *in vitro* conditions. Understanding this effect is essential to ensure that the antibacterial benefits of Chi-AgNPs do not compromise cellular viability and bone regeneration potential. The objective of this study is to evaluate the effect of Chi-AgNPs on the viability of preosteoblast *MC3T3-E1* cells *in vitro*. This research also aims to analyze the relationship between different concentrations of Chi-AgNPs and cell viability in order to identify concentration ranges that are biocompatible and suitable for further biomedical application. The findings of this study are expected to provide scientific evidence supporting the safe development of Chi-AgNPs as a potential biomaterial for bone-related therapies.[10]

RESEARCH METHOD

This study employed a laboratory experimental in vitro design using a post-test only control group approach to evaluate the effect of Chitosan–Silver Nanoparticles (Chi-AgNPs) on the viability of preosteoblast *MC3T3-E1* cells. This study has obtained a certificate of ethical feasibility from the Health Research Ethics Commission of the Faculty of Dentistry, Brawijaya University Number 062/UN10.F1301/KEPK-FKGUB/EC08/2025. The experimental design was selected to allow direct comparison between treated and untreated groups following nanoparticle exposure.

Preosteoblast *MC3T3-E1* cells were cultured in α-Minimum Essential Medium (α-MEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin, and maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cells in the logarithmic growth phase and free from contamination were used as research samples. After reaching approximately 80–90% confluence, cells were seeded into 96-well plates at a density of 1×10^4 cells per well and incubated for 24 hours prior to treatment.[11]

Chi-AgNPs were synthesized using a green synthesis method, in which *Clinacanthus nutans* extract acted as a reducing agent and chitosan functioned as a stabilizing agent. Silver nitrate ($AgNO_3$) solution (0.001 M) was reacted with plant extract under continuous stirring until a color change indicated nanoparticle formation. The resulting silver nanoparticles were subsequently combined with 1% chitosan solution, centrifuged, dried, and resuspended in phosphate-buffered saline (PBS). Transmission Electron Microscopy (TEM) was used for nanoparticle characterization, revealing an average particle size of 20 ± 3.93 nm, indicating successful nanoscale synthesis.[12–14]

The experimental groups consisted of a cell control group containing MC3T3-E1 preosteoblast cells in untreated culture medium, a media control group containing cell culture medium without any treatment, and three treatment groups exposed to Chi-AgNPs at concentrations of 12.5 µg/mL, 25 µg/mL, and 50 µg/mL, respectively. All treatments were applied for 24 hours under identical incubation conditions. Cell viability was evaluated using the WST assay, which measures mitochondrial metabolic activity based on the reduction of water-soluble tetrazolium salt into formazan, with absorbance measured at 450 nm using an ELISA reader.

Data were analyzed statistically using SPSS software. Normality and homogeneity of variance were assessed prior to inferential analysis. Differences in cell viability among groups were analyzed using one-way ANOVA, followed by Tukey's HSD post hoc test to identify significant intergroup differences. A p-value < 0.05 was considered statistically significant.

RESULTS

Chi-AgNPs at a concentration of 12.5 µg/mL and incubated for 24 hours showed an increase in viability of 30.8% compared to the control group, indicating that cells can proliferate in Chi-AgNPs at a concentration of 12.5 µg/mL. Cells exposed to Chi-AgNPs at a concentration of 25 µg/mL for 24 hours did not show any statistically significant difference from the control group cells. In contrast, exposure to Chi-AgNPs at a higher concentration (50 µg/mL) resulted in a significant reduction in cell viability compared to the control and lower concentration groups. Statistical analysis using one-way ANOVA followed by post hoc testing confirmed that this decrease was statistically significant ($p < 0.05$), indicating a cytotoxic effect at higher concentrations.

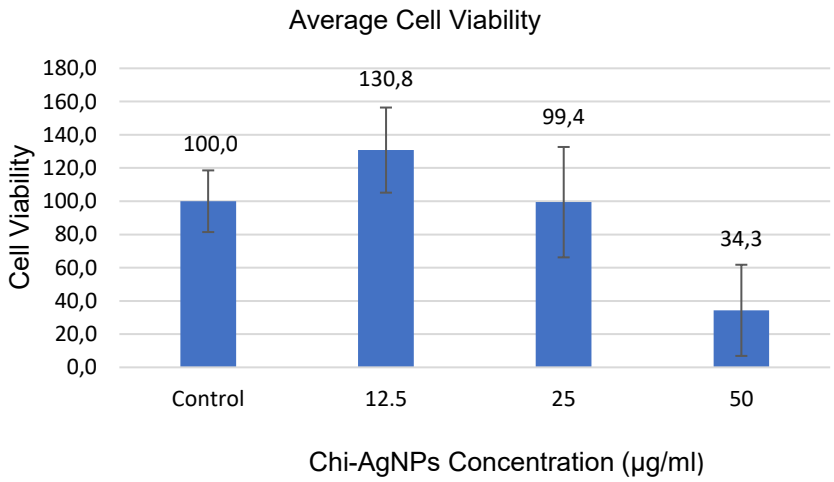

Figure 1. Average Cell Viability

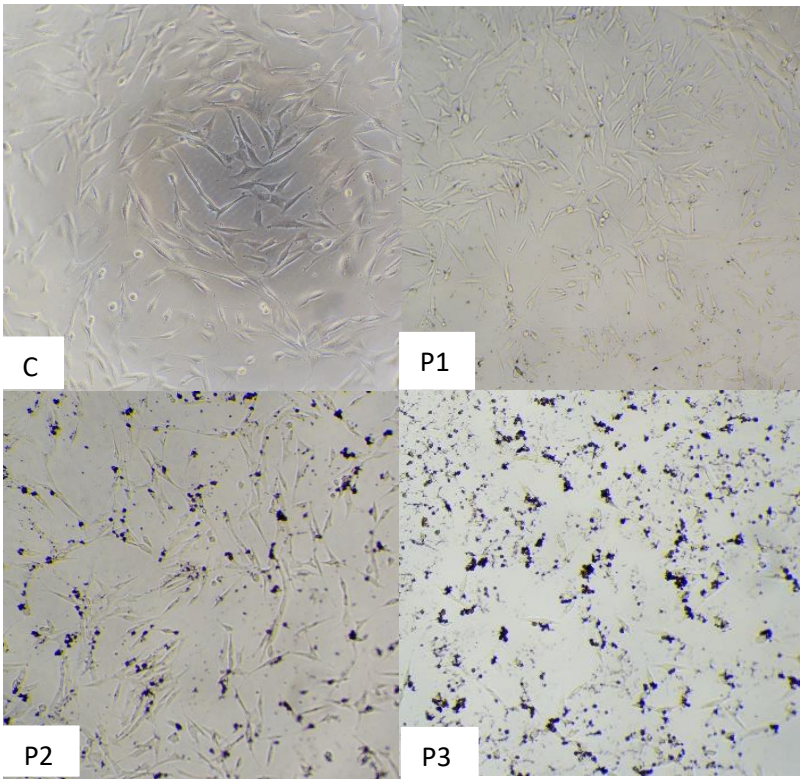

Figure 2. MC3T3-E1 preosteoblast cell culture observed under an inverted microscope (C). After treatment with Chi-AgNPs at a concentration of 12.5 µg/mL and incubation for 24 hours (P1). After treatment with Chi-AgNPs at a concentration of 25 µg/mL and incubation for 24 hours (P2). After treatment with Chi-AgNPs at a concentration of 50 µg/mL and incubation for 24 hours (P3).

Table 1. Normality test

	p	
Control	0.582	Normal
12.5 Concentration	0.218	Normal
25 Concentration	0.111	Normal
50 Concentration	0.109	Normal

Table 2. One way ANOVA test

	Viability	F	Significance
Control	100	11.536	<0.001
12.5 Concentration	130.8		
25 Concentration	99.4		
50 Concentration	34.3		

Table 3. Post hoc Tukey HSD test

	C	P1	P2	P3
C		0.3	1	**0.006**
P1			0.286	<**0.001**
P2				**0.007**
P3				

Based on the table, it can be concluded that the 50 µg/ml concentration group has a significant difference compared to the 25 µg/ml concentration group and the 12.5 µg/ml concentration group. The 12.5 µg/ml concentration group experienced an increase in the average viability value, but it was not yet significant.

DISCUSSION

This study demonstrated that Chitosan–Silver Nanoparticles (Chi-AgNPs) influenced the viability of preosteoblast *MC3T3-E1* cells in a concentration-dependent manner, biotoxicity of Ag ions is highly dependent on dosage. One possible strategy to control related cytotoxicity is to provide a controlled release design for AgNP-based coatings on implant surfaces.[15] Specifically, chitosan, which can be obtained from chitin, has been widely used in the field of biomaterial design and surface modification. One of the most important aspects of chitosan is its action as an ideal chelating agent for Ag ions.[4] The findings confirm that Chi-AgNPs can exhibit both biocompatible and cytotoxic effects depending on the concentration used, which is consistent with the fundamental principles of nanoparticle–cell interactions.[16,17]

Previous research on silver nanoparticles (AgNPs) has shown that the Minimum Inhibitory Concentration (MIC) for many oral anaerobic pathogenic bacteria such as *Streptococcus mutans* and *Aggregatibacter actinomycetemcomitans* falls between 25 and 50 µg/mL. Research specifically focusing on the MC3T3-E1 preosteoblast cell line indicates that concentrations below 25 µg/mL are optimal for supporting cell viability and proliferation. At 12.5 µg/mL, AgNPs are typically considered a low concentration that has no significant toxic effects on various human cell lines, including dental pulp stem cells and gingival fibroblasts. By testing these three concentration, the study can determine if the material can successfully kill bacteria at the same concentrations where it remains safe for bone-forming cell. MC3T3-E1 preosteoblast cell cultures observed under an inverted microscope demonstrated a progressive, likely dose-dependent, cytotoxic effect of specific treatments across the three groups. Group C served as a healthy control, displaying high cell density with normal, elongated, spindle-shaped cells forming an interconnected network. As the groups progressed from P1 to P3, there was a sequential decrease in cell health and density due to the treatments. Group P1 showed a moderate decrease in density and slight rounding of cells, indicating initial stress, while Group P2 showed a much lower density, a severe loss of normal spindle morphology, and a clearly visible accumulation of dark cell

debris or test material. Group P3 showed massive cell death and detachment, with almost no healthy cells remaining and the field of view completely dominated by fragmented dark debris, confirming that increasing treatment concentrations were toxic to MC3T3-E1 preosteoblast cell cultures.[9,17]

The research indicates a clear dose-dependent response of MC3T3-E1 cells to Chi-AgNPs, establishing a distinct boundary between bio-stimulation and cytotoxicity. At a concentration of 12.5 µg/mL, viability increases by 30.8%, likely due to the chitosan coating enhancing cell adhesion and mitochondrial activity while minimizing reactive oxygen species (ROS) production, all while maintaining an effective antibacterial silver dose. As the concentration reaches 25 µg/mL, the cells enter a critical transition phase. Although there is a slight increase in oxidative stress and a dip in mitochondrial enzyme activity, the protective properties of chitosan keep viability above the 70% benchmark set by ISO 10993-5, thus maintaining its biocompatible status. However, once the concentration hits 50 µg/mL, viability plummets to 34.3%, falling well below the ISO threshold and classifying the material as definitively toxic. At this high dose, the protective capacity of chitosan is overwhelmed by the silver nanoparticles, leading to severe mitochondrial membrane damage, ATP depletion, and the initiation of apoptosis through excessive ROS production.[18,19]

Chi-AgNPs enter cells through endocytosis, and these particles are usually trapped in vesicles such as endosomes and lysosomes.[20] Although chitosan helps maintain particle stability, Chi-AgNPs can still release silver ions (Ag^+) in the cellular environment. These ions are highly reactive and can interfere with various proteins and membrane components.[21] The interaction of silver ions with cell structures is one of the initial triggers of oxidative stress. An increase in free radicals or reactive oxygen species (ROS) is the root cause of almost all toxic effects of silver nanoparticles, including Chi-AgNPs. When ROS production exceeds the cell's antioxidant defense capacity, cell membranes become more fragile, proteins begin to oxidize, and DNA becomes more susceptible to damage.[22–24] Mitochondria are one of the organelles most affected by increased ROS. Chi-AgNPs can cause a decrease in mitochondrial membrane potential, disrupt cellular respiration, and reduce energy production.[25] This damage often leads to the release of cytochrome-c, which is an important signal in the activation of the apoptosis pathway. When mitochondria lose their function, cells find it difficult to return to their normal state, resulting in a significant decrease in viability at excessively high doses of Chi-AgNPs.[26]

The implications of this research are centered on the discovery of a specific therapeutic window for Chitosan-Silver Nanoparticles (Chi-AgNPs) in bone tissue engineering. At a low concentration of 12.5 µg/mL, the nanoparticles significantly boost the viability of MC3T3-E1 cells by 30.8%, suggesting that they could be used to actively stimulate bone cell growth and accelerate healing in clinical applications like dental implants or bone grafts. However, the research also establishes a clear safety ceiling. As concentrations reach 50 µg/mL, the material becomes highly cytotoxic, killing over 65% of the cells. This confirms that while Chi-AgNPs have great potential as a bioactive and antimicrobial agent, their clinical success depends entirely on precise dosage control to avoid irreversible tissue damage. Despite these promising results, the research is limited by its short-term, in-vitro scope, as the 24-hour incubation period does not account for the long-term cumulative effects of silver in a living organism. Furthermore, while the study proves the cells remain alive at lower concentrations, it does not provide functional data to confirm that these cells are still capable of producing bone matrix and mineralizing.

CONCLUSION

Chitosan–Silver Nanoparticles (Chi-AgNPs) significantly influence the viability of preosteoblast *MC3T3-E1* cells in a concentration-dependent manner under *in vitro* conditions. Low concentrations of Chi-AgNPs (12.5 µg/mL) enhanced cell viability, while moderate concentrations (25 µg/mL) maintained viability without causing a significant difference compared to the control group. In contrast, high concentrations of Chi-AgNPs (50 µg/mL) resulted in a significant reduction in cell viability, indicating cytotoxic effects. Statistical analysis confirmed significant differences among treatment groups ($p < 0.001$) and demonstrated that increasing Chi-AgNP concentration was associated with decreased cell viability. To advance this research, further studies should focus on uncovering the molecular mechanisms of toxicity and bone formation through ROS, apoptosis, and gene expression assays (such as Runx2 and ALP) while extending incubation periods to evaluate long-term biocompatibility. Additionally, transitioning from 2D cultures to 3D scaffolds and in vivo animal models is essential to validate the material's clinical efficacy and safety for real-world orthopedic or dental applications.

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