

Original Article

Regenerative Effects of α -Mangostin-Loaded ZnO Nanoparticles on Wound Healing: *In Vitro* and Zebrafish *In Vivo* Insights

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Mangostin, a key bioactive compound derived from the peel of *Garcinia mangostana*, is known for its wound-healing potential. This study aims to evaluate the combinatorial therapeutic effects of α -Mangostin-derived zinc oxide nanoparticles (α -mangostin-ZnO NPs) on wound healing, with emphasis on antimicrobial, anti-inflammatory, antioxidant, and molecular mechanisms. α -mangostin-ZnO nanoparticles were synthesized via alkaline precipitation of zinc acetate, with α -mangostin serving as a bioactive surface-functionalizing and stabilizing agent rather than a reducing agent. The nanoparticles were assessed using *in vitro* antimicrobial assays against wound-associated pathogens. Anti-inflammatory activity was evaluated by protein denaturation inhibition, and antioxidant potential was assessed using hydroxyl radical scavenging assays. *In silico* molecular docking was performed using α -mangostin as the ligand alone, due to current limitations in modelling inorganic nanoparticle-protein interfaces. *In vivo* wound-healing efficacy was examined using a zebrafish wound model. α -mangostin-ZnO NPs exhibited enhanced antimicrobial activity compared to amoxicillin at higher concentrations. RT-PCR analysis showed regulated expression of pro-inflammatory markers (MMP13, TNF- α , and IL-1 β), particularly at Day 14 post-injury, indicating accelerated inflammatory resolution. The findings demonstrate that α -mangostin-ZnO NPs act as a multifunctional wound-healing nanoplatform through integrated antimicrobial, antioxidant, and anti-inflammatory mechanisms.

Introduction

Wound healing is a complex and dynamic process that involves a series of coordinated biological events, including haemostasis, inflammation, cell proliferation, and tissue remodelling [1]. These stages are essential for restoring the integrity of damaged tissues and ensuring effective recovery. Despite notable advancements in medical treatments, managing chronic wounds - those that do not progress through the normal stages of healing - continues to be a significant challenge, highlighting the need for innovative therapeutic strategies. Chronic wounds are often complicated by persistent infections, prolonged inflammation, and impaired tissue regeneration, which demand advanced solutions capable of addressing these multifaceted issues [2].

Recent developments in nanomedicine have highlighted the potential of α -mangostin-ZnO NPs as novel agents for wound healing management. This combination harnesses the individual advantages of α -

mangostin and zinc oxide nanoparticles to tackle the diverse challenges associated with wound healing. The unique properties of α -mangostin-ZnO NPs may enhance the healing process through their antibacterial, anti-inflammatory, and antioxidant effects, positioning them as promising candidates for the treatment of chronic wounds [3]. α -Mangostin-ZnO NPs have emerged as an innovative therapeutic approach in wound healing, integrating the unique biological activities of both α -mangostin and zinc oxide nanoparticles (ZnO NPs). ZnO NPs are renowned for their exceptional antibacterial properties, which are essential for preventing infections in chronic wounds. Their ability to reduce bacterial load is particularly important, as infections often complicate and hinder the healing process. In addition to their antimicrobial effects, ZnO NPs also exhibit anti-inflammatory properties that help regulate the inflammatory response, thus reducing excessive inflammation that can delay recovery. Furthermore, these nanoparticles possess antioxidant capabilities that combat oxidative stress, a factor detrimental to cellular health

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and wound healing. By promoting fibroblast proliferation and facilitating collagen synthesis, ZnO NPs play a crucial role in forming new connective tissue, ensuring tissue strength and integrity [4].

Complementing these advantages, α -mangostin is a natural polyphenolic compound known for its wide range of biological activities [5]. It provides antioxidative, antimicrobial, and anti-inflammatory benefits and has traditionally been used in herbal medicine to support healing. α -mangostin effectively scavenges free radicals, reducing oxidative stress and preventing cellular damage. Its potent antimicrobial properties extend to a variety of pathogens, including those resistant to antibiotics, making it a valuable tool in managing wound infections. Additionally, α -mangostin helps regulate inflammatory pathways by inhibiting the production of pro-inflammatory cytokines and enzymes, thereby enhancing its efficacy in controlling inflammation associated with wounds. Studies have shown that α -mangostin-ZnO NPs can significantly enhance wound healing outcomes. For instance, these nanoparticles have been reported to expedite the healing of diabetic wounds, which are particularly challenging due to compromised immune responses and inadequate circulation. α -mangostin-ZnO NPs have exhibited the ability to promote re-epithelialization, aiding the migration of new epithelial cells to cover wounds while effectively reducing bacterial load [6]. Their effectiveness has also been assessed in the context of burn wound healing, where α -mangostin-ZnO NPs were found to decrease inflammation and facilitate faster tissue regeneration compared to conventional therapies. The potential of α -mangostin-ZnO NPs is not only promising but also underscores the necessity of exploring their synergistic effects when combined with other therapeutic agents. This combined effect reflects the enhanced therapeutic outcomes observed when α -mangostin-ZnO NPs are administered alongside additional treatments, resulting in greater efficacy than when the components are used individually. Understanding these interactions is crucial for the development of more effective wound healing therapies that capitalize on the strengths of α -mangostin-ZnO NPs. To further investigate these effects, the zebrafish model provides an excellent *in vivo* system for evaluating the impact of α -mangostin-ZnO NPs on wound healing in a living organism. Zebrafish are particularly advantageous for biomedical research due to their genetic similarities to humans, rapid wound healing capabilities, and transparent embryos that enable real-time observation of healing processes [7]. This study aims to evaluate the efficacy of α -mangostin-ZnO NPs in promoting wound closure, tissue regeneration, and reduction of inflammation, thereby providing insights into their potential mechanisms of action. The underlying hypothesis of this research posits that α -mangostin-ZnO NPs, especially when combined with other therapeutic agents, will significantly enhance the wound healing process. This enhancement may occur through various mechanisms, such as the combined antimicrobial effects of α -mangostin-ZnO NPs with additional antibacterial agents, concurrent anti-inflammatory actions with other anti-inflammatory drugs, or a synergistic promotion of collagen synthesis alongside other regenerative compounds. Exploring these interactions could lead to innovative wound management strategies that surpass the effectiveness of current treatments [5].

Research indicates that α -mangostin-ZnO NPs possess robust antimicrobial activity against a wide range of microorganisms, including bacteria, fungi, and viruses. This broad-spectrum efficacy is especially valuable in combating pathogenic microorganisms, providing both preventive and therapeutic applications. Studies have demonstrated that α -mangostin-ZnO NPs can inhibit the growth of antibiotic-resistant strains, presenting a promising alternative in an era marked by increasing antimicrobial resistance. Moreover, the anti-inflammatory properties of α -mangostin-ZnO NPs further enhance their therapeutic profile. By modulating inflammatory pathways and inhibiting the production of pro-inflammatory cytokines and enzymes, these nanoparticles may help alleviate chronic inflammatory conditions. Evidence from various animal models supports the efficacy of α -mangostin-ZnO NPs in reducing inflammation, indicating their potential usefulness in treating conditions such as inflammatory bowel disease and arthritis. In the realm of herbal medicine, α -mangostin-ZnO NPs are increasingly utilized for their diverse therapeutic effects, often in combination with other bioactive compounds to improve efficacy. Their integration into modern formulations

for skin health showcases their versatility. For example, topical preparations containing α -mangostin-ZnO NPs have been developed for treating acne and eczema, capitalizing on their antioxidative and antimicrobial properties. Clinical trials have demonstrated significant reductions in acne lesions and improvements in skin texture, highlighting their potential in dermatological applications [8].

Chronic wounds, particularly diabetic ulcers and biofilm-associated infections, remain a major clinical challenge due to persistent inflammation, microbial colonization, and oxidative stress. These pathological features delay re-epithelialization and extracellular matrix remodeling. Therefore, therapeutic strategies that simultaneously target microbial burden, inflammatory dysregulation, and oxidative stress are critically required. The wide array of biological activities exhibited by α -mangostin-ZnO NPs - including antioxidative, antimicrobial, and anti-inflammatory effects - makes them a highly versatile compound with numerous applications in medicine. The rising interest in natural products, coupled with the demand for effective, safe, and sustainable therapeutic agents, highlights the necessity for further research into the potential of α -mangostin-ZnO NPs. As our understanding of their mechanisms improves, α -mangostin-ZnO NPs are likely to play a significant role in the development of innovative treatments for a variety of health conditions, ranging from chronic inflammatory diseases and skin health. The ongoing exploration of their applications in both traditional and modern medicine holds great promise for advancing natural therapeutic strategies that cater to the increasing demand for health products derived from nature. This study aims to rigorously examine the synergistic effects of α -mangostin-ZnO NPs on wound healing through a combination of *in vitro* assays and zebrafish model studies, ultimately providing valuable insights into their efficacy and potential clinical applications [5,9].

Materials and Methods

Preparation of α -mangostin-ZnO NPs

α -Mangostin-ZnO NPs are synthesized by dissolving 24.55 g of zinc acetate dihydrate ($\text{Zn}(\text{CH}_3\text{CO}_2)_2 \cdot 2\text{H}_2\text{O}$) in 100 ml of deionized water to create a 0.1 M solution. Concurrently, 4 g of sodium hydroxide (NaOH) is dissolved in 100 ml of deionized water to prepare another 0.1 M solution. α -Mangostin was incorporated during synthesis as a bioactive capping and surface-functionalizing molecule. ZnO formation occurred through alkaline precipitation of zinc acetate using NaOH. No metallic zinc formation was involved in this process. The zinc acetate solution is then added dropwise to the sodium hydroxide solution while stirring vigorously. The mixture is heated until a white precipitate forms, indicating the formation of the nanoparticles. After cooling, the precipitate is collected through centrifugation and washed with ethanol and deionized water to remove impurities. The resulting α -mangostin-ZnO NPs are then dried and characterized using various techniques. Fourier Transform Infrared Spectroscopy (FTIR) analysis is conducted by preparing a pellet of the nanoparticles for examination with an FTIR spectrometer. X-ray Diffraction (XRD) analysis is performed on a powdered sample of the nanoparticles. Lastly, UV analysis involves dispersing the nanoparticles in ethanol and measuring the absorbance spectrum using a UV-Vis spectrophotometer [5,9,10].

In vitro anti-inflammatory and antioxidant analysis

Albumin inhibition assay

To evaluate the inhibition of albumin denaturation, a stock solution of human serum albumin (HSA) was prepared by dissolving it in phosphate buffer at pH 7.4 to achieve a concentration of 5 mg/ml. Concurrently, the synthesized α -mangostin-ZnO NPs were dispersed in an appropriate solvent to reach the desired concentration. Test solutions of anti-inflammatory agents were then created by diluting them in the phosphate buffer. In a series of test tubes, equal volumes of the HSA solution, the test compounds, and the nanoparticle dispersion were mixed and incubated at a controlled temperature of 37°C for one hour. A separate set of HSA tubes underwent the same incubation conditions without the nanoparticles, serving as a positive control for denaturation.

Following the incubation period, the samples were allowed to cool and then subjected to heat stress by heating at 70°C for 20 minutes. The absorbance of each sample was then measured at 660 nm using a UV-Vis spectrophotometer. A decrease in absorbance in the samples containing α -mangostin-ZnO NPs, compared to the control, indicated inhibition of albumin denaturation, suggesting the potential anti-inflammatory properties of the nanoparticles [11].

Hydroxyl radical scavenging assay

A reaction mixture was prepared that included a hydroxyl radical source, specifically Fenton's reagent (a 1:1 mixture of 10 mM FeSO₄ and 10 mM H₂O₂ solutions), along with varying concentrations of α -mangostin-derived zinc oxide nanoparticles (α -mangostin-ZnO NPs). The reaction mixture was incubated at room temperature. To initiate the reaction between the hydroxyl radicals and salicylic acid, salicylic acid was added, leading to the formation of 2,3-dihydroxybenzoic acid. After the incubation period, the reaction was halted by adding trichloroacetic acid (TCA), followed by the introduction of thiobarbituric acid (TBA) to produce a pink chromogen. The tubes were then heated, allowed to cool, and subsequently centrifuged. Finally, the absorbance of the supernatant was measured at a wavelength of 532 nm using a UV-Vis spectrophotometer to evaluate the progress of the reaction.

Minimum inhibitory concentration

Each pathogen - *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus* - was cultured separately in the appropriate growth media until reaching mid-log phase. The cultures were then diluted to obtain a standardized bacterial suspension of approximately 5 x 10⁶ CFU/mL. A series of dilutions of the α -mangostin-ZnO NPs stock solution were prepared in the respective growth media to cover a range of concentrations.

In a 96-well microplate, aliquots of the bacterial suspension were dispensed into each well, followed by the addition of different concentrations of α -mangostin-ZnO NPs. Positive and negative controls were included, with amoxicillin serving as the positive control and an untreated sample as the negative control. The microplate was then incubated at the appropriate temperatures for each pathogen (37°C for *S. aureus* and *E. coli*, 42°C for *V. vulnificus*, and 30°C for *P. aeruginosa*) for 18-24 hours. After incubation, bacterial growth was assessed either visually or by measuring optical density at a suitable wavelength using a microplate reader. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of α -mangostin-ZnO NPs at which no visible growth or a significant decrease in optical density was observed compared to the control [12].

Zone of inhibition

In the well diffusion method, agar plates were prepared by pouring molten agar containing the appropriate growth media for each pathogen, such as nutrient agar for *S. aureus* and *E. coli*, Mueller-Hinton agar for *P. aeruginosa*, and tryptic soy agar supplemented with 2% NaCl for *V. vulnificus*. Once solidified, bacterial suspensions of 5 x 10⁶ CFU/mL were evenly spread across the surface of the agar plates using a sterile swab. Wells were then created in the agar using a sterile cork borer, and various concentrations of the α -mangostin-ZnO NPs solution were added to the wells. Amoxicillin was included as a positive control, along with an untreated control. The plates were incubated at room temperature, and after incubation, the zones of inhibition around the wells containing α -mangostin-ZnO NPs were measured in millimeters (mm) using a calibrated ruler [13].

Ligand and receptor interaction studies

The experimental procedure began with retrieving crystal structures of receptors relevant to *S. aureus*, *E. coli*, *P. aeruginosa*, and *V. vulnificus* from the Protein Data Bank (<https://www.rcsb.org/>). PyMOL (<https://pymol.org/>) was used to prepare these receptor structures by removing water molecules and non-essential ligands. The 3D structure of α -mangostin alone was used for docking analysis, as current computational platforms do not allow accurate simulation of inorganic nanoparticle-protein interactions. Docking parameters were set, and binding affinity was evalu-

ated by analysing the results, including binding energy and interaction patterns. Finally, Discovery Studio Visualizer software was used to visualize the 3D and 2D binding interactions between α -mangostin-ZnO NPs and the receptor proteins.

In vivo studies

Zebrafish toxicity

All zebrafish experiments were conducted following approval from the Institutional Animal Ethical Committee of Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS) (Approval No.: BRULAC/SDCH/SIMATS/IAEC/06-2023/15). The zebrafish were acclimatized in a controlled aquatic environment maintained at a temperature of 28°C ± 1°C, with a pH range of 7.0-7.5 and a 14:10 light-dark cycle. During the acclimatization period, the zebrafish were housed in 10 L glass tanks filled with dechlorinated water, equipped with aeration and filtration systems. After a one-week acclimatization phase to ensure physiological adjustment, the zebrafish were randomly assigned to experimental groups, each consisting of 6 individuals to enable adequate statistical analysis. The experimental groups were exposed to varying concentrations of α -mangostin-ZnO NPs, ranging from 40 µg/mL to 80 µg/mL. Throughout the one-week exposure period, the survival rates of the zebrafish were monitored daily and calculated as the percentage of surviving zebrafish relative to the total number in each group at the start of the experiment.

Zebrafish wound closure experiments

In the *in vivo* wound healing experiment, zebrafish (n=6/group) were divided into four groups: a control group, wounded zebrafish, and two experimental groups treated with α -mangostin-ZnO NPs at concentrations of 40 µg/mL and 80 µg/mL, respectively. The fish were anesthetized by immersion in a 0.2% Tricaine methane sulfonate solution before being wounded with a sterilized scalpel behind the gill region, near the lateral line. The post-opercular lateral trunk region was selected for wound induction as it is rich in fibroblasts and epidermal progenitor cells, supports angiogenesis assessment, and is associated with minimal mortality. Fish were monitored twice daily, and humane endpoints included >20% body weight loss, abnormal swimming behavior, loss of equilibrium, excessive hemorrhage, or impaired feeding. The α -mangostin-ZnO NPs were administered to the wounded zebrafish every third day, and the healing process was monitored through daily photographs. Zebrafish were anesthetized at specific intervals (0, 7, and 14 days post-injury), and the wounded sites were photographed and analysed for closure using ImageJ software. The progress of wound healing was assessed by periodically measuring the wound area, with injured locations identified by observing differences in skin color between affected and unaffected regions. Healing progression continued to be tracked until the wounded area fully regenerated and returned to its original coloration, indicating the completion of the healing process [14].

Gene expression studies

Adult zebrafish were categorized into four groups: treatment 1 (α -mangostin-derived zinc oxide nanoparticles at 40 µg/mL), treatment 2 (α -mangostin-ZnO NPs at 80 µg/mL), model (wounded zebrafish), and unwounded control. Tissue samples from the wounded area were collected and stored at -80°C. The pooled wound tissue underwent homogenization using a Polytron PT 1200E (Kinematic, Switzerland) for RNA isolation with TRIzol reagent (Invitrogen, Carlsbad, CA, USA). The RNA concentration was determined using a NanoDrop One, followed by cDNA synthesis using 2.5 µg of the isolated RNA and a PrimeScript 1st strand cDNA synthesis kit (TaKaRa®, Tokyo, Japan) according to the manufacturer's instructions. The synthesized cDNA samples were diluted 30-fold with nuclease-free water and stored at -20°C until further analysis. The primers utilized in this study are detailed in table 1, with zebrafish β -actin serving as the housekeeping gene. Quantitative real-time PCR (qRT-PCR) was performed using a Thermal Cycler Dice Real-Time System (TaKaRa®) following a previously published protocol with minor modifications. Each qRT-PCR reaction consisted of 3 µL of cDNA template, 1 µL (10 µM) of each forward and reverse

Table 1: Primers used for gene expression

Primers used for gene expression	Forward primer (5'-3')	Reverse primer (5'-3')	Accession number
MMP13	GAGAAGGTTTGGGCTCTCTATG	TGAGTTGCTGTCTTCCTTGTAG	AF506756
TNF- α	AGAAGGAGAGTTGCCTTTACCGCT	AACACCCTCCATACACC CGACTTT	AF025305
IL-1 β	TCAAACCCCAATCCACAGAG	TCACTTCACGCTCTTGGA TG	AY340959.1
β actin	AATCTTGCGGTATCCACGAGACCA	TCTCCTTCTGCATCCTGT CAGCAA	AF025305

primer, and 5 μ L of TB Green Premix Ex Taq II (TaKaRa®) qPCR mix. Primer specificity was confirmed through a standard three-step thermal cycling profile with an annealing temperature of 56°C, followed by a single dissociation reading step. Relative expression fold changes were calculated using the 2- $\Delta\Delta$ CT method [15].

Statistical analysis

Statistical analyses were conducted using GraphPad Prism software (Version 8, San Diego, CA, USA). To evaluate the significance between the control and treated groups, one-way analysis of variance (ANOVA) was employed, followed by Tukey's post hoc test. A significance threshold of $p < 0.05$ was established, and all data are presented as mean $\pm$ standard deviation.

Results

The characterization results indicate that the α -mangostin-ZnO NPs possess distinct structural and chemical properties. FTIR analysis identifies characteristic peaks at wave numbers 1644.96, 1353.42, 1204.72, 1025.82, 888.15, 761.99 and 541.38, indicating the presence of functional groups associated with both α -mangostin and zinc oxide (figure 1). These peaks correspond to various chemical bonds and molecular vibrations, offering insight into the composition and bonding within the α -mangostin-ZnO NPs. Crystallite size was calculated using the Scherrer equation applied to the (101) diffraction peak, yielding an average crystallite size of approximately 21–25 nm, consistent with SEM observations. The relatively high amorphous percentage (69.9%) likely

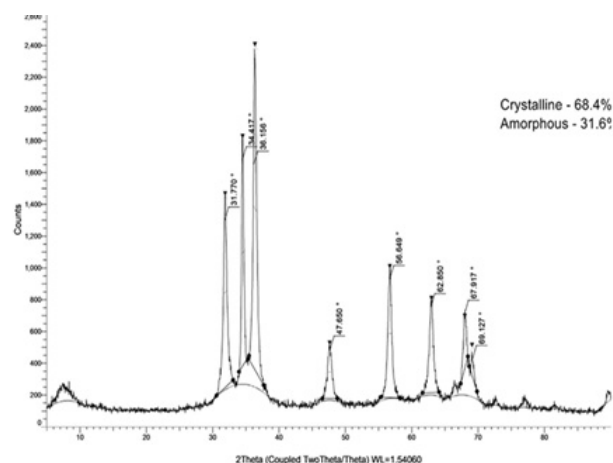


Figure 2: XRD analysis of α -Mangostin-ZnO NPs illustrating the presence of a crystalline phase and amorphous phase

reflects the thick organic coating of α -mangostin rather than intrinsic ZnO structural disorder. UV-Vis spectroscopy showed a dominant absorption peak at 268 nm, corresponding primarily to π - π electronic transitions of α -mangostin polyphenolic moieties adsorbed on the nanoparticle surface. The characteristic ZnO excitonic absorption band ($\sim$ 360–380 nm) appeared as a broad shoulder, likely masked due to ex-

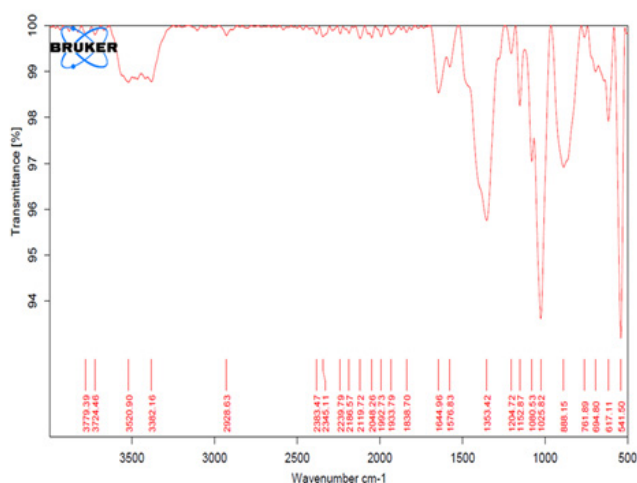


Figure 1: FTIR spectrum represent specific vibrational modes corresponding to functional groups present in the α -mangostin-ZnO NPs

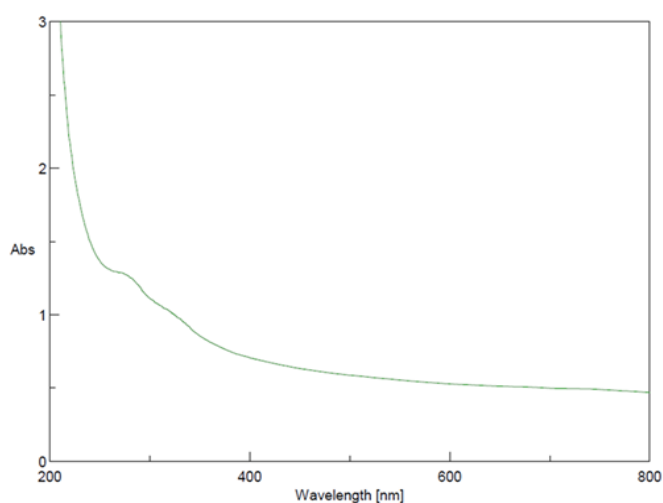


Figure 3: UV-Vis spectrum of synthesized α -Mangostin-ZnO NPs

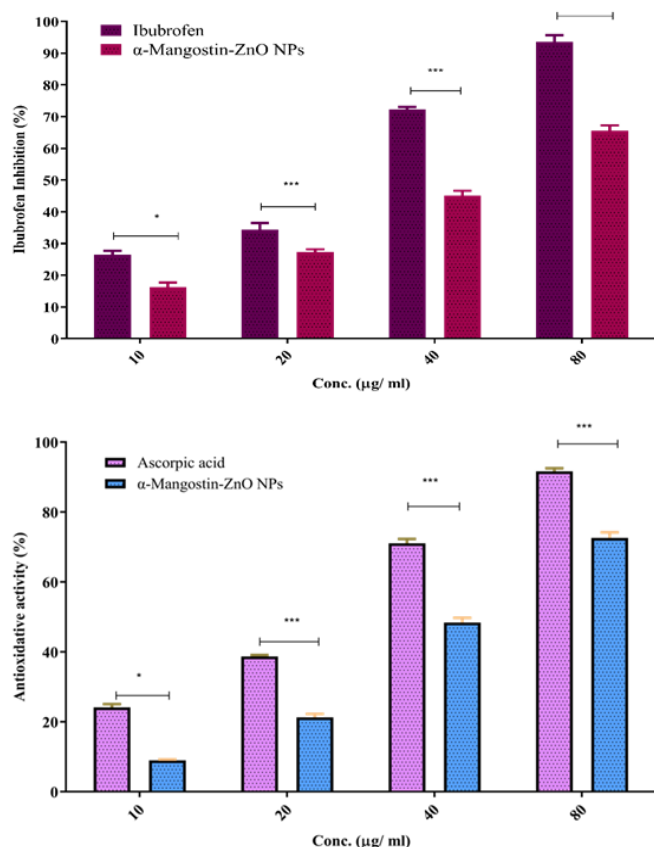


Figure 4: (A) Albumin denaturation Inhibition and (B) Hydroxyl radical scavenging activity of α-Mangostin-ZnO NPs at different concentrations (10 µg/mL, 20 µg/mL, 40 µg/mL, and 80 µg/mL). Diclofenac and Trolox was used as a positive control. The * represented the level of significance ($p < 0.05$) when the results were compared to the control. Data were presented as mean $\pm$ SD of three independent experiments**

tensive organic surface functionalization (figure 3).

Inhibition of albumin denaturation and free radical scavenging activity

The results of the study on α-mangostin-ZnO NPs indicate promising properties in combating protein denaturation and oxidative stress. In the albumin denaturation experiment, α-mangostin-ZnO NPs at the higher concentration of 80 µg/mL exhibited 63% activity, which is slightly lower than the positive control, ibuprofen, showing 72% activity. This suggests that α-mangostin-ZnO NPs effectively prevent protein denaturation in a manner similar to diclofenac. Similarly, in the hydroxyl radical scavenging assay, α-mangostin-ZnO NPs at 80 µg/mL demonstrated 69% activity, comparable to the positive control, ascorbic acid, which exhibited 75% activity. These results indicate that α-mangostin-ZnO NPs possess significant antioxidant capabilities, effectively neutralizing harmful hydroxyl radicals. Overall, these findings suggest that α-mangostin-ZnO NPs hold promise as therapeutic agents for addressing conditions related to protein misfolding and oxidative damage (figure 4).

Inhibition of biofilm formation

The MIC experiment with α-mangostin-ZnO NPs demonstrated their effectiveness against a variety of pathogenic bacteria, including *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus*. The MIC values were consistently recorded at 40 µg/mL for all tested bacteria, indicating that concentrations at or above this threshold significantly ($p < 0.05$) inhibited bacterial growth (figure 5). This underscores the broad-spectrum antimicrobial activity of α-mangostin-ZnO NPs across both gram-positive and gram-negative bacteria. Furthermore, the zone of inhibition assay confirmed the antimicrobial potential of α-mangostin-ZnO NPs. At a concentration of 80 µg/mL, the NPs produced inhibition zones measuring 7 mm, 6 mm, 4 mm, and 8 mm against *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus*, respectively. Increasing the concentration to 80 µg/mL resulted in larger zones of inhibition (8 mm, 10 mm, 5 mm, and 7 mm), demonstrating a dose-dependent response (table 2). Notably, the zones of inhibition exceeded those of the positive control, amoxicillin (50 µg/mL), indicating that at 80 µg/mL, the antimicrobial activity of α-mangostin-ZnO NPs significantly outperformed that of amoxicillin against all tested pathogens (figure 6).

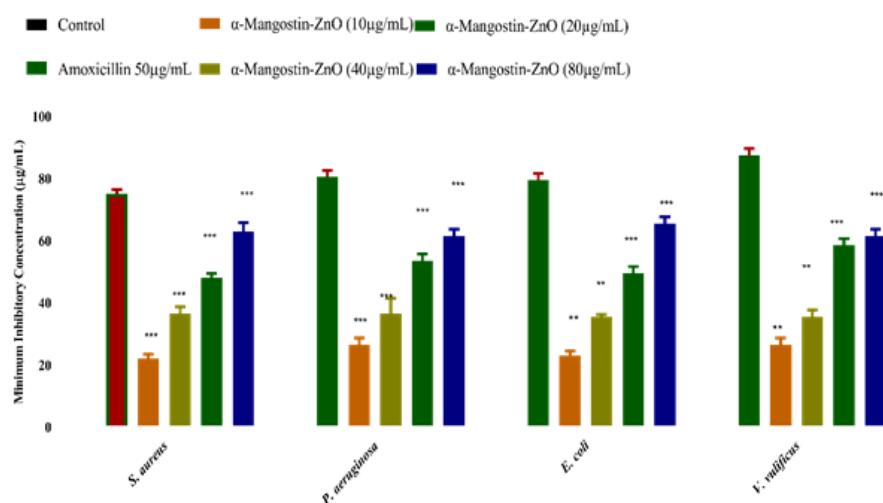


Figure 5: MIC of α-Mangostin-ZnO NPs at different concentration against dental pathogens of *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus*. Amoxicillin was used as positive control. The * represented the level of significance ($p < 0.05$) when the results were compared to the control. Data were presented as mean $\pm$ SD of three independent experiments**

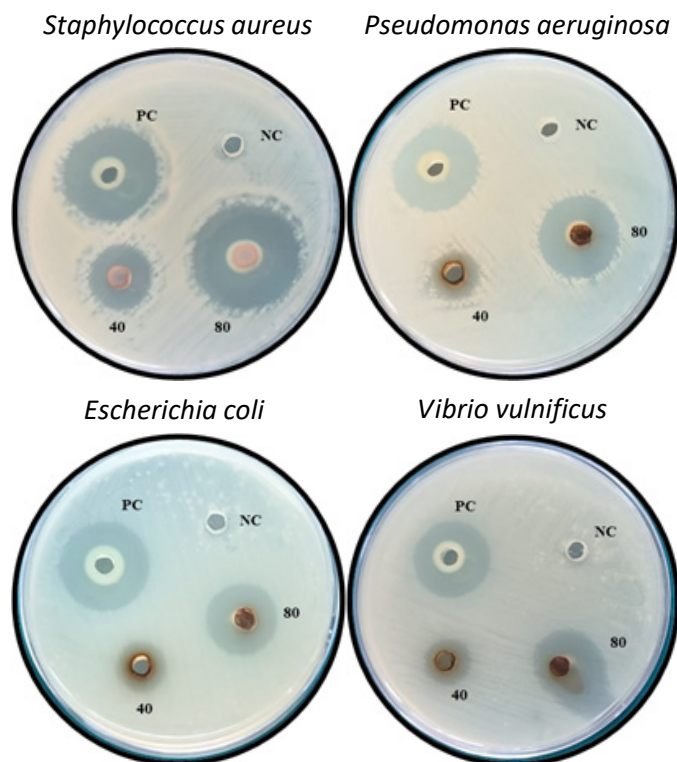


Figure 6: Zone of inhibition of different dental pathogen by α -Mangostin-ZnO NPs (A): Control, (B): Amoxicillin (50 μ g/mL), at 40 μ g/mL, and (D): α -Mangostin-ZnO NPs at 80 μ g/mL.

Binding interaction with pathogenic receptor

Mangostin exhibits varying binding affinities with different bacterial receptors. In the *S. aureus* Sortase A-substrate complex (PDB: 7S53), it binds with an affinity of -5.2 kcal/mol, interacting with amino acids such as GLU, LEU, ALA, VAL, LYS, and MET, which likely stabilizes the ligand and inhibits Sortase A activity. In *P. aeruginosa* LasR (PDB: 4NG2), mangostin has a binding affinity of -4.6 kcal/mol, with interactions involving PHE, TYR, GLU, and GLY, suggesting potential π - π stacking that disrupts LasR's signalling pathway (table 3). For *E. coli*'s outer membrane porin (PDB: 2OMF), mangostin shows a strong affinity of -5.5 kcal/mol, interacting with a diverse set of amino acids, including PRO, ALA, GLY, HIS, LEU, and LYS, indicating it may affect membrane permeability or nutrient uptake. Lastly, in the *V. vulnificus* nuclear protein (PDB: 5TV2), mangostin binds with an affinity of -4.4 kcal/mol, interacting with LYS, ARG, and MET, which could suggest a role in modulating nuclear functions (figure 7).

Survival rate analysis in zebrafish

The study examined the toxicity of α -mangostin-ZnO NPs on zebrafish,

comparing four groups: a control group (unwounded fish), wounded zebrafish, and zebrafish treated with varying concentrations of α -mangostin-ZnO NPs. The results indicated a 69% decrease in survival rate among the wounded zebrafish, highlighting the potential adverse effects of injury. Notably, zebrafish exposed to α -mangostin-ZnO NPs at concentrations of 40 μ g/mL and 80 μ g/mL showed no significant toxicity compared to the control group. This suggests that within the tested concentrations, α -mangostin-ZnO NPs do not pose considerable toxicity to zebrafish (figure 8).

Wound healing activity

The wound healing activity of α -mangostin-ZnO NPs was investigated on wounded zebrafish, focusing on concentrations of 40 μ g/mL and 80 μ g/mL over periods of 7 and 14 days post-wounding (dpw). Notably, treatment with α -mangostin-ZnO NPs at 40 μ g/mL resulted in a 54% closure of wounds at 7 dpw, while at 80 μ g/mL, the closure significantly increased to 62% ($p < 0.05$). Remarkably, by 14 dpw, the closure rates further improved to 70% and 93% for the 40 μ g/mL and 80 μ g/mL concentrations, respectively, compared to the control group. These findings underscore the potential efficacy of α -mangostin-ZnO NPs in promoting accelerated wound closure in zebrafish models, suggesting their promise for further exploration in wound healing applications (figure 9).

Wound morphological analysis

Histological analysis of wounded zebrafish tissue revealed distinct differences across various groups: (A) Control (unwounded zebrafish), (B) wounded Zebrafish, (C) α -mangostin-ZnO NPs treatment at 40 μ g/mL, and (D) α -mangostin-ZnO NPs treatment at 80 μ g/mL. The tissue layers examined included skeletal muscle, dermal layer, granulation tissue, and epithelial layer with immune cell infiltration. Microscopic examination of zebrafish treated with α -mangostin-ZnO NPs, compared to the untreated control group, revealed notable differences in tissue composition. The treated groups exhibited a densely layered epidermis, significant proliferation of granulation tissue, and clear formation of new blood vessels (neoangiogenesis). Remarkably, the treated zebrafish displayed rapid development of a thin layer of new epidermis just hours after nanoparticle application. Additionally, the presence of abundant dispersed fibroblasts within the pronounced granulation tissue, along with an influx of inflammatory cells, indicated an active healing process facilitated by the nanoparticles. This was further supported by the emergence of newly formed vasculature, signifying an accelerated healing response. The enhanced wound healing induced by α -mangostin-ZnO NPs was evident in the treated group's significantly quicker wound contraction and the formation of fresh scales within an impressive timeframe of 4 to 6 days post-wound creation, contrasting sharply with the slower healing observed in the untreated control group (figure 10).

Expression level of wound healing related genes

To understand the molecular mechanism of α -mangostin-ZnO NPs treatment in wound healing, the gene expression levels of matrix metalloproteinase 13 (MMP13) and pro-inflammatory cytokines such as TNF- α and IL-1 β were evaluated. The higher concentration of α -mangostin-ZnO NPs at 80 μ g/mL was selected for further gene expression studies due to its observed superior activity and lower toxicity.

Table 2: Zone of inhibition (mm)

Bacterial Strain	Control (mm)	Amoxicillin (50 μ g/ml)	α -Mangostin-ZnO NPs (40 μ g/ml)	α -Mangostin-ZnO NPs (80 μ g/ml)
<i>Staphylococcus aureus</i>	12	9	10	7
<i>Pseudomonas aeruginosa</i>	13	10	9	9
<i>Escherichia coli</i>	13	8	6	10
<i>Vibrio vulnificus</i>	11	6	8	5

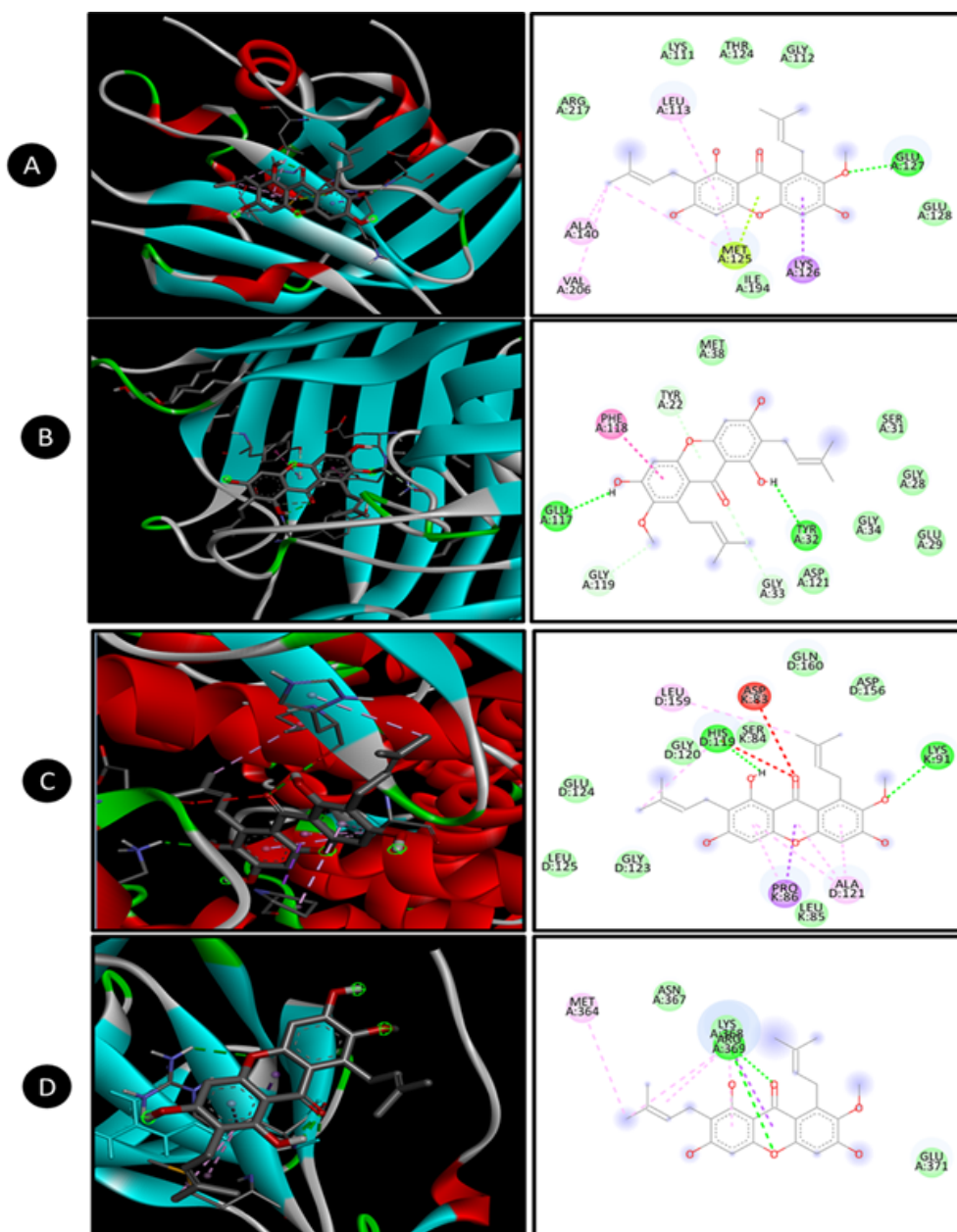


Figure 7: 3D and 2D interaction images of Mangostin and wound-infecting bacterial pathogens. (A) 7S53 (antimicrobial protein), (B) 4NG2 (oxidative stress regulator), (C) 20MF (inflammatory mediator), (D) 5TV2 (wound healing protein). The interaction is observed with amino acids such as GLU (Glutamic acid), LEU (Leucine), ALA (Alanine), VAL (Valine), LYS (Lysine), MET (methionine), PHE (Phenylalanine), TYR (Tyrosin), GLY (glycine), PRO (proline), HIS (Histidine), ARG (Arginine)

The results showed that the wound-administered group demonstrated a significant upregulation in the gene expression of MMP13 (3.5-fold), TNF- α (5.7-fold), and IL-1 β (4.6-fold). In contrast, the expression levels of MMP13 (1.7-fold), TNF- α (3.4-fold), and IL-1 β (2.3-fold) were significantly downregulated in the α -mangostin-ZnO NPs treated group (80 μ g/mL) compared to the control group (figure 11).

Discussion

The emergence of α -mangostin-ZnO NPs as a novel therapeutic strategy for wound healing highlights the innovative combination of ZnO NPs with α -mangostin, utilizing their distinct biological activities to tackle

the complex challenges of wound management. ZnO NPs are well-known for their potent antibacterial properties, crucial for preventing infections, which are a significant barrier to healing in chronic wounds [16]. Their effectiveness in reducing bacterial load is enhanced by anti-inflammatory effects that help regulate the inflammatory response, thereby minimizing delays in healing caused by excessive inflammation. Additionally, their antioxidant capabilities are vital in countering oxidative stress, which can negatively impact cellular health and hinder recovery. When paired with α -mangostin, a natural polyphenolic compound recognized for its wide range of biological activities, the wound healing potential is further amplified. α -mangostin not only provides antioxidative, antimicrobial, and anti-inflammatory benefits but also ef-

Table 3: Amino acid and Binding affinity value of the vanillic acid interaction with different dental pathogen receptors as GLU (Glutamic acid), LEU (Leucine), ALA (Alanine), VAL (Valine), LYS (Lysine), MET (methionine), PHE (Phenylalanine), TYR (Tyrosin), GLY (glycine), PRO (proline), HIS (Histidine), ARG (Arginine)

Receptor (PDB ID)	Ligand	Binding affinity (kcal/mol)	Amino acid interaction
<i>S. aureus</i> : Sortase A-substrate Complex (SrtA) (PDB: 7S53)	Mangostin	-5.2	GLU, LEU, ALA, VAL, LYS, MET
<i>P. aeruginosa</i> : LasR (PDB: 4NG2)	Mangostin	-4.6	PHE, TYR, GLU, GLY
<i>E. coli</i> : Outer membrane porin (integral membrane protein porin) (PDB: 2OMF)	Mangostin	-5.5	PRO, ALA, GLY, HIS, LEU, LYS
<i>V. vulnificus</i> : Nuclear Protein (PDB: 5TV2)	Mangostin	-4.4	LYS, ARG, MET

fectively scavenges free radicals, reducing oxidative damage. This enhanced efficacy between ZnO NPs and α -mangostin presents a promising path for advancing wound healing therapies, addressing both infection control and tissue regeneration [17].

Characterization of α -mangostin-ZnO NPs reveals critical structural and chemical properties essential for potential applications in wound healing. In this study, the promising antioxidant and anti-inflammatory therapeutic potential of α -mangostin-ZnO NPs in wound healing can be attributed to their ability to stabilize proteins and scavenge harmful oxidative agents. By preventing protein denaturation, these NPs help maintain cellular integrity in the wound environment, reducing inflam-

mation in a manner similar to established anti-inflammatories like diclofenac. Their significant antioxidant activity also alleviates oxidative stress -a key barrier to healing - by neutralizing reactive oxygen species (ROS) that can damage tissue at the wound site. These functionalities not only accelerate the healing process but also enhance tissue repair, corroborated by previous studies indicating that *Aerva persica*-mediated synthesis of ZnO NPs demonstrated a dual therapeutic effect of antioxidant and anti-inflammatory properties [18].

The superior antimicrobial activity of α -mangostin-ZnO NPs compared to amoxicillin may be attributed to ZnO-mediated reactive oxygen species (ROS) generation, disruption of bacterial membrane integ-

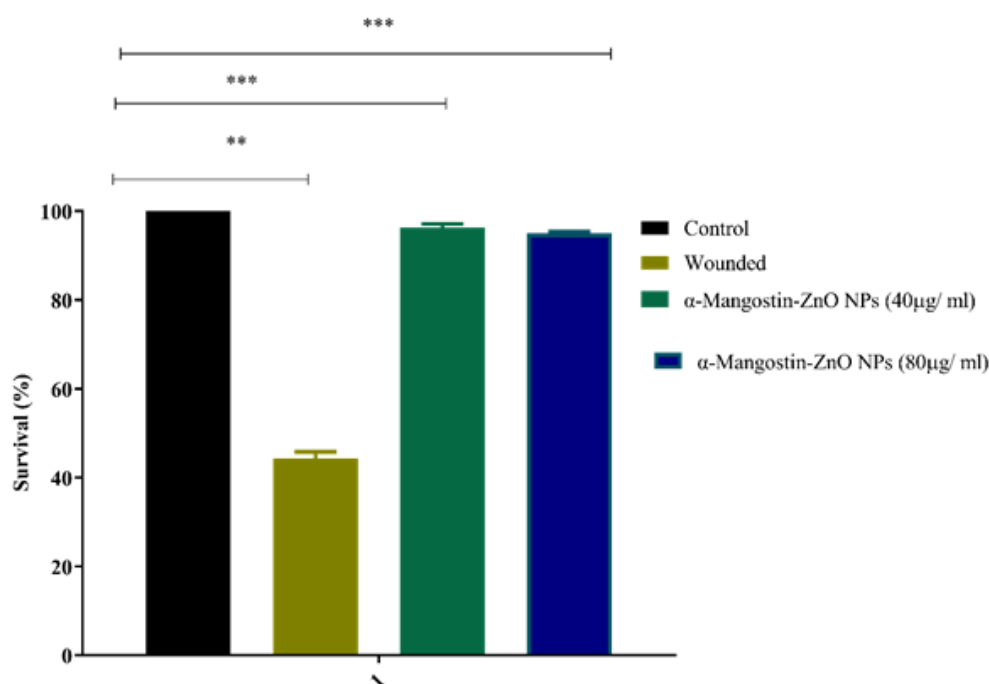


Figure 8: The survival rate analysis of zebrafish with different groups of control, wounded zebrafish, and exposure to α -Mangostin-ZnO NPs (40 μ g/mL and 80 μ g/mL). The independent three experimental data were expressed as mean $\pm$ SD (n=6/group). The significant difference at $p < 0.05$ was expressed as *

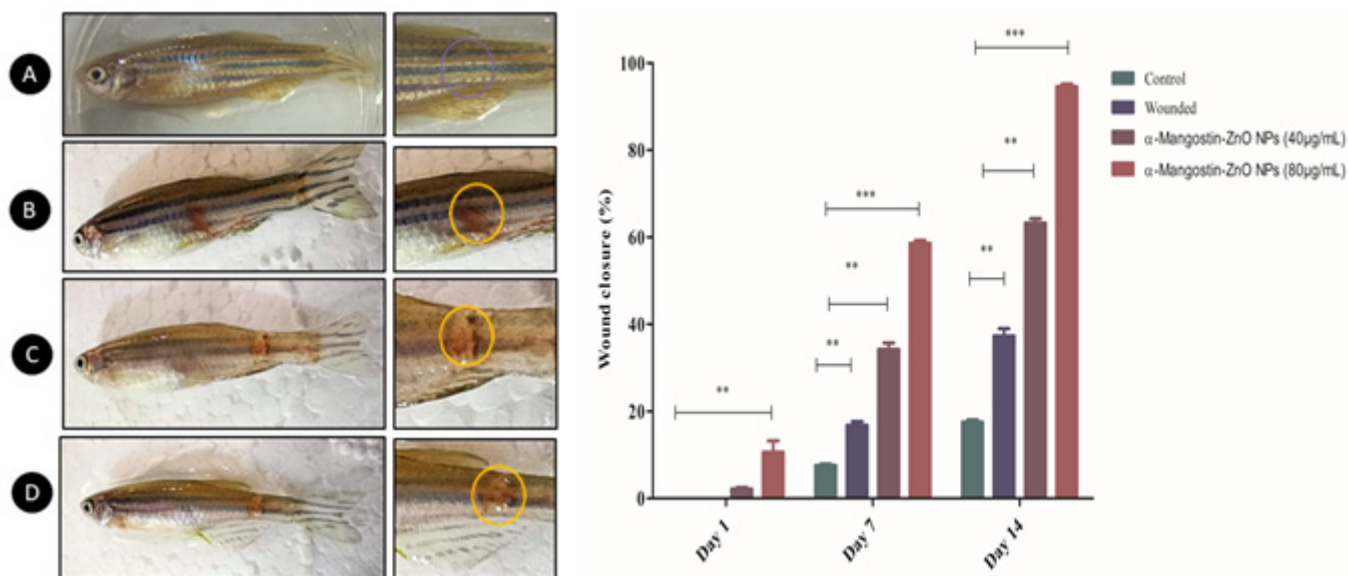


Figure 9: (A – D) Representative photograph of wounded zebrafish treated with α -Mangostin-ZnO NPs at different concentrations. (E) The graphical presentation of the wound closure was measured using Image J software. The independent three experimental data were expressed as mean $\pm$ SD (n=6/group). The significant difference at $p < 0.05$ was expressed as **

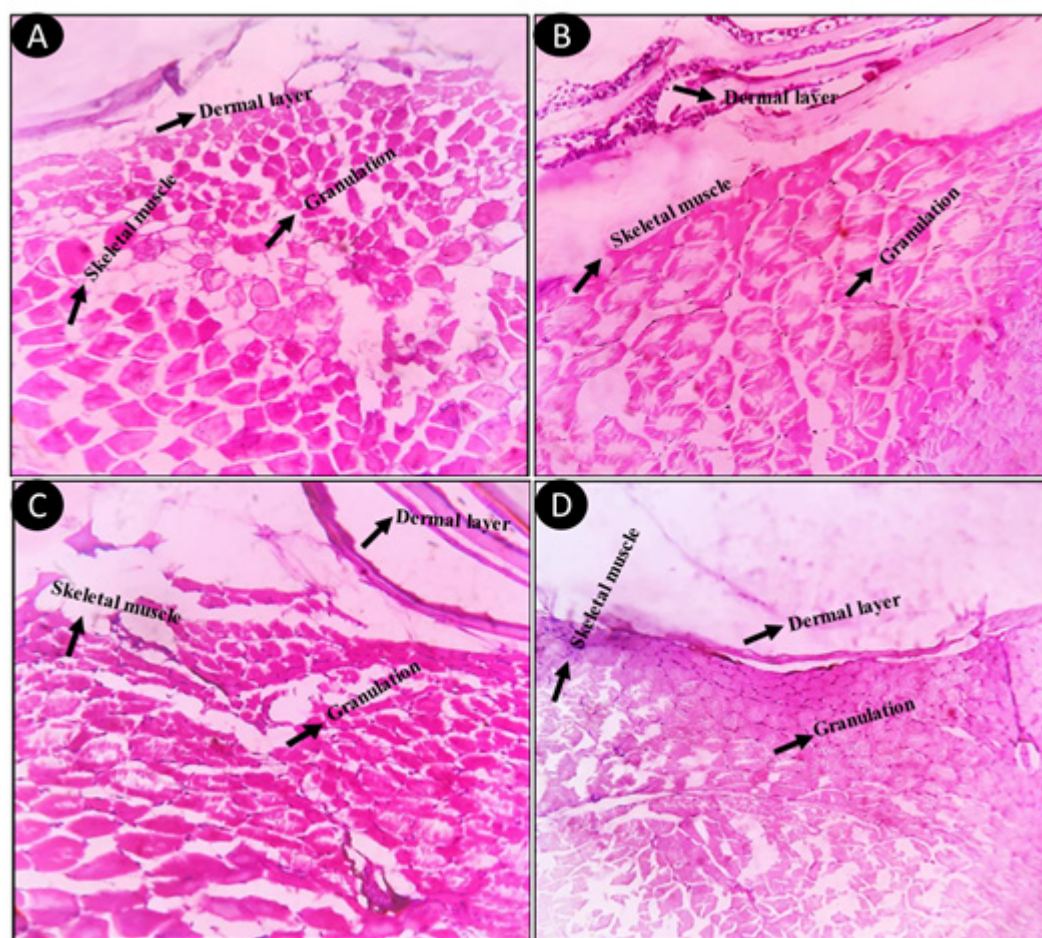


Figure 10: Histological analysis of wounded zebrafish tissue. (A) Control (unwounded zebrafish), (B) Wounded Zebrafish, (C) α -Mangostin-ZnO NPs treatment at 40 μ g/mL, and (D) α -Mangostin-ZnO NPs treatment at 80 μ g/mL. The tissue layers include skeletal muscle, dermal layer, granulation tissue, and epithelial layer with immune cell infiltration

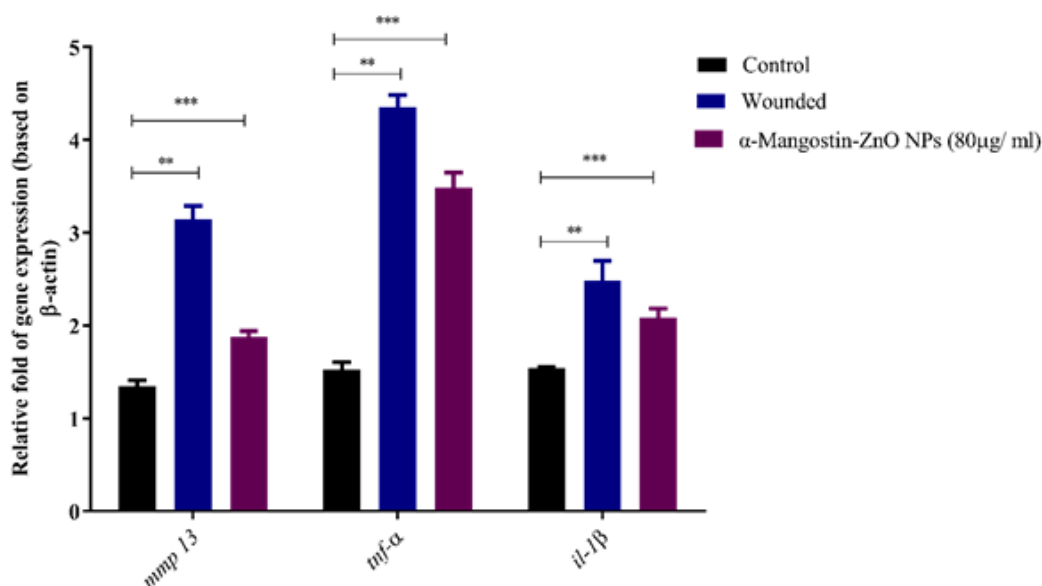


Figure 11: Effect of α -Mangostin-ZnO NPs treatment group on the mRNA expression level of *MMP13*, *TNF- α* , *IL-1 β* . Data were expressed as mean $\pm$ SD of three independent experiments. * $p < 0.05$ as compared to the control

rity, nanoparticle penetration through extracellular polymeric substance (EPS) matrices, and sustained surface-associated α -mangostin release. Unlike β -lactam antibiotics, ZnO nanoparticles bypass classical resistance mechanisms by inducing oxidative membrane damage. Infections can delay healing by causing inflammation, increasing necrotic tissue burden, and disrupting new tissue formation. Effective antimicrobial agents speed up the healing process by maintaining a cleaner wound environment while minimizing the potential for developing antibiotic resistance, a significant concern with traditional antimicrobial treatments. This antimicrobial efficacy is critical in preventing and controlling infections at wound sites, particularly against common pathogens such as *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus*. The ability of α -mangostin-ZnO NPs to inhibit the growth of both gram-positive and gram-negative bacteria makes them excellent candidates for topical wound dressings and coatings that require robust antimicrobial properties [19].

In the context of wound infections, the Sortase A-substrate complex (SrtA) in *S. aureus* is significant because it facilitates the attachment of surface proteins, including adhesins and toxins, to the bacterial cell wall. This attachment is essential for *S. aureus* to adhere to and invade host tissues, initiating infection. Adhesins enable bacteria to adhere to damaged tissues and host cells at the wound site, promoting colonization and biofilm formation, which can protect bacteria from host defenses and antibiotics. Additionally, toxins anchored to the cell wall by SrtA can damage host cells and tissues, contributing to the pathogenesis of *S. aureus* infections [20].

One of the key virulence factors of *P. aeruginosa* in wound infections is the LasR protein, a transcriptional regulator controlling the expression of numerous virulence genes. *P. aeruginosa* is adept at forming biofilms, complex communities of bacteria encased in a matrix of extracellular polymeric substances. LasR regulates the expression of genes involved in biofilm formation, promoting attachment to wound surfaces and protecting bacteria from host immune defenses and antibiotics. In *E. coli*, the outer membrane porin OmpC contributes to its virulence in wound infections by allowing the passage of small molecules, including nutrients, toxins, and antibiotics, into the bacterial cell. This can enhance the pathogenicity of *E. coli* in wound infections, facilitating the uptake of toxic substances produced by the host or promoting antibiotic resistance [21].

In *V. vulnificus* wound infections, the protein EpsD is involved in the biosynthesis of extracellular polysaccharides (EPS), a crucial com-

ponent of the bacterial biofilm matrix. This protein enables biofilm formation on both biotic and abiotic surfaces, including wounds. Biofilms are complex communities of bacteria encased in a self-produced matrix of EPS, proteins, and DNA, which provides structural support and protects bacteria from environmental stresses, including host immune responses and antibiotic treatments. EpsD is essential for EPS synthesis and secretion, contributing to the stability of *V. vulnificus* biofilms on wound surfaces [22].

In this study, α -mangostin, which demonstrated significant binding affinity to essential bacterial proteins like Sortase A in *S. aureus*, LasR in *P. aeruginosa*, OmpC in *E. coli*, and EpsD in *V. vulnificus*, offers promising prospects for clinical applications in preventing wound infections. These compounds could serve as lead molecules for novel antimicrobial therapeutics, complementing existing treatments or being formulated into topical preparations and wound dressings for direct application. Through their ability to disrupt key virulence factors and inhibit biofilm formation, α -mangostin-ZnO NPs hold potential for enhancing wound healing and reducing infection risk, particularly in high-risk populations or clinical settings where infection control is critical.

Wound healing is essential for restoring the structural and functional integrity of tissues, promoting overall patient health and well-being. Proper wound closure reduces the risk of infection, prevents further tissue damage, and facilitates the restoration of normal physiological function, allowing patients to resume their daily activities more quickly. Previous studies have explored the wound healing activity of nano emulsions with *Elaeis guineensis* leaf extract in zebrafish models, observing effective wound closure after treatment. Similarly, our study's results regarding the toxicity analysis and wound healing activity of α -mangostin-ZnO NPs in zebrafish models present significant implications for potential applications in wound management. The absence of discernible toxicity in zebrafish, even at concentrations as high as 80 μ g/mL, underscores the favourable safety profile of α -mangostin-ZnO NPs. This finding is particularly promising, suggesting that these nanoparticles may be well-tolerated in biological systems, a crucial consideration for any therapeutic intervention [23].

Furthermore, the remarkable wound healing activity observed with α -mangostin-ZnO NPs highlights their potential as effective wound healing agents. Concentrations of 40 μ g/mL and 80 μ g/mL demonstrated accelerated wound closure compared to the control group, with the higher concentration showing particularly notable results, achieving

a closure rate of 93% by 14 days post-wounding. Additionally, tissue repair during the wound healing process was confirmed through histological examination, revealing the development of skeletal muscle, dermal layer, granulation tissue, and epithelial layer with immune cell infiltration. This accelerated wound closure suggests that α -mangostin-ZnO NPs promote tissue regeneration and repair, potentially enhancing the overall wound healing process. These findings open exciting possibilities for developing α -mangostin-ZnO NPs-based wound dressings or topical formulations for clinical use.

Tissue samples for gene expression analysis were collected at Day 14 post-injury. Therefore, the observed downregulation of inflammatory markers reflects accelerated resolution of inflammation rather than suppression of the initial inflammatory phase. In the context of wound healing, MMP13 and pro-inflammatory cytokines TNF- α and IL-1 β play significant roles. While MMP13 is essential for early extracellular matrix remodeling, its prolonged overexpression contributes to pathological tissue degradation in chronic wounds. The moderated expression observed in treated groups suggests restoration of physiological remodeling balance rather than complete inhibition. MMP13 activity promotes the breakdown of damaged tissue and the migration of inflammatory cells to the wound site, aiding in tissue repair. Tnf- α and IL-1 β induce the expression of adhesion molecules and chemokines, recruiting leukocytes and amplifying the inflammatory cascade. Moreover, IL-1 β stimulates fibroblast proliferation and collagen synthesis, promoting tissue repair. Together, these molecules orchestrate various phases of wound healing, from inflammation to tissue remodelling [24].

According to earlier reports, downregulation of MMP13, TNF- α , and IL-1 β was observed during the wound healing process in zebrafish models. In line with this, our study's upregulation of these genes in the wound-administered group indicates an active inflammatory phase necessary for initiating the healing process. However, the downregulation of these genes in the α -mangostin-ZnO NPs treated group suggests modulation of the inflammatory response, potentially leading to a more controlled and efficient healing process. These findings highlight the therapeutic potential of α -mangostin-ZnO NPs in wound management by regulating inflammatory signalling pathways and promoting tissue repair. This study did not include individual ZnO-only and α -mangostin-only treatment groups across all assays, limiting definitive claims regarding molecular combined effects. Future studies should incorporate these controls to quantitatively establish synergistic interactions using combination index analysis.

Conclusion

In conclusion, the promising findings regarding α -mangostin-ZnO NPs highlight their potential as effective agents in wound healing through their antimicrobial, anti-inflammatory, and antioxidant properties. The observed mechanisms suggest that these nanoparticles can modulate inflammatory responses while promoting tissue regeneration, paving the way for innovative therapeutic approaches. Future studies should include mono-component ZnO and α -mangostin controls to mechanistically validate potential synergistic interactions. Additionally, investigating the mechanisms underlying their interactions with bacterial virulence factors will be crucial for developing targeted treatments. Overall, α -mangostin-ZnO NPs hold significant promise for enhancing wound care strategies in both clinical and community settings.

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