

Original Article

Evaluating the Combined Effects of Zinc Oxide and Hamamelitannin Nanoparticles on Wound Healing: Results from *In vitro* and Zebrafish Experiments

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This study evaluates the wound-healing efficacy of zinc oxide nanoparticles functionalized with hamamelitannin (ZnO–HM NPs), focusing on their antimicrobial, antioxidant, anti-inflammatory, and regenerative properties through integrated *in vitro* and zebrafish *in vivo* models. ZnO nanoparticles were synthesised via alkaline precipitation and subsequently surface-functionalized with hamamelitannin, which served as a bioactive stabilising ligand. Antimicrobial assays demonstrated significant inhibitory activity of ZnO–HM NPs against wound-associated pathogens including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Vibrio vulnificus*, showing enhanced efficacy compared to amoxicillin. Anti-inflammatory activity assessed by albumin denaturation revealed substantial protein stabilisation, while hydroxyl radical scavenging confirmed strong antioxidant potential. Molecular docking was performed using hamamelitannin to predict ligand–protein interactions with key bacterial and inflammatory targets, supporting its biological contribution to the composite system. *In vivo* zebrafish wound models showed accelerated closure and tissue regeneration following ZnO–HM NP treatment. Quantitative RT-PCR analysis of wound tissues collected on Day 14 post-injury demonstrated significant downregulation of pro-inflammatory markers (MMP13, TNF- α , and IL-1 β), indicating resolution-phase modulation of inflammation. Collectively, these findings suggest that ZnO–HM NPs exhibit enhanced combined therapeutic efficacy through antimicrobial activity, regulation of oxidative stress, and control of inflammation, highlighting their promise as multifunctional, nano-enabled wound-healing agents.

Introduction

Wound healing is an intricate and a dynamic process involving coordinated biological events such as haemostasis, inflammation, cell proliferation, and tissue remodelling. These stages are crucial for restoring the integrity of damaged tissues and ensuring proper recovery [1]. Despite significant progress in medical treatments, the management of chronic wounds that fail to progress through the normal stages of healing remains a persistent challenge, underscoring the need for innovative therapeutic approaches. Chronic wounds are often complicated by persistent infections, prolonged inflammation, and impaired tissue regeneration, necessitating advanced solutions that can effectively address these hurdles [2]. Recent advancements in nanomedicine have underscored the potential of Hamamelitannin derived zinc nanoparticles (ZnO–HM NPs) as innovative agents in wound healing management.

This combination leverages the individual strengths of zinc oxide nanoparticles and Hamamelitannin, to address the multifaceted challenges associated with wound healing. The unique properties of ZnO–HM NPs may enhance the healing process through their antibacterial, anti-inflammatory, and antioxidant effects, making them promising candidates for treating chronic wounds [3].

ZnO–HM NPs have emerged as a novel therapeutic strategy in wound healing, combining the distinct biological activities of Zinc Oxide Nanoparticles (ZnO NPs) and Hamamelitannin. ZnO NPs are well-known for their remarkable antibacterial properties, crucial for preventing infections in chronic wounds. Their ability to minimize bacterial load is particularly significant, as infections are a common complication that can hinder healing [4]. Additionally, ZnO NPs possess anti-inflammatory effects that help modulate the inflammatory response, reducing excessive inflammation that can delay the healing process. These

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nanoparticles also exhibit antioxidant capabilities, counteracting oxidative stress, which is detrimental to cellular health and wound recovery. By promoting fibroblast proliferation and enhancing collagen synthesis, ZnO NPs play a vital role in forming new connective tissue, thus ensuring tissue strength and integrity [5]. Complementing these benefits, Hamamelitannin is a natural polyphenolic compound recognized for its broad spectrum of biological activities. It offers antioxidative, antimicrobial, and anti-inflammatory properties, traditionally utilized in herbal medicine for promoting healing. Hamamelitannin scavenges free radicals, mitigating oxidative stress and preventing cellular damage. Its strong antimicrobial effects extend to a wide range of pathogens, including antibiotic-resistant strains, making it a valuable asset in managing wound infections. Furthermore, Hamamelitannin modulates inflammatory pathways by inhibiting the production of pro-inflammatory cytokines and enzymes, enhancing its effectiveness in controlling inflammation associated with wounds.

Studies indicate that ZnO-HM NPs can significantly improve wound healing outcomes [6]. For example, these nanoparticles have been reported to accelerate the healing of diabetic wounds, which are notoriously challenging due to impaired immune responses and poor circulation. ZnO-HM NPs have demonstrated their ability to enhance reepithelialization, the migration of new epithelial cells to cover the wound, while also effectively reducing bacterial load. Their efficacy has also been explored in burn wound healing, where ZnO-HM NPs were found to reduce inflammation and promote faster tissue regeneration compared to conventional treatments [7].

The potential of ZnO-HM NPs is not only promising but also highlights the importance of investigating their enhanced combined efficacy when combined with other therapeutic agents. This enhanced combined efficacy refers to the enhanced therapeutic outcomes observed when ZnO-HM NPs are used alongside additional treatments, resulting in improved efficacy over individual components. Understanding these interactions is crucial for developing more effective wound healing therapies that harness the strengths of ZnO-HM NPs. To explore these effects further, the zebrafish model serves as an excellent *in vivo* system for evaluating the impact of ZnO-HM NPs on wound healing in a living organism. Zebrafish are advantageous for biomedical research due to their genetic similarities to humans, rapid wound healing capabilities, and transparent embryos that allow real-time observation of healing processes. This study aims to assess the efficacy of ZnO-HM NPs in promoting wound closure, tissue regeneration, and inflammation reduction, providing insights into their potential mechanisms of action. The underlying hypothesis of this research posits that ZnO-HM NPs, particularly when combined with other therapeutic agents, will significantly enhance the wound healing process. This enhancement could occur through various mechanisms, such as the combined antimicrobial effects of ZnO-HM NPs with additional antibacterial agents, concurrent anti-inflammatory actions with other anti-inflammatory drugs, or synergistic promotion of collagen synthesis alongside other regenerative compounds [8]. Investigating these interactions may lead to innovative wound management strategies that surpass the effectiveness of current treatments. Research has shown that ZnO-HM NPs possess strong antimicrobial activity, extending across bacteria, fungi, and viruses. This broad-spectrum efficacy is particularly valuable in combating pathogenic microorganisms, providing both preventive and therapeutic applications. Studies have indicated that ZnO-HM NPs can inhibit the growth of antibiotic-resistant strains, offering a promising alternative in an era where antimicrobial resistance is a growing concern [9].

Moreover, the anti-inflammatory properties of ZnO-HM NPs further enhance their therapeutic profile. By modulating inflammatory pathways and inhibiting pro-inflammatory cytokines and enzymes, these nanoparticles may alleviate chronic inflammatory conditions. Evidence from various animal models supports the efficacy of ZnO-HM NPs in reducing inflammation, indicating their potential utility in treating conditions like inflammatory bowel disease and arthritis. In herbal medicine, ZnO-HM NPs are increasingly utilized for their multifaceted therapeutic effects, often in combination with other bioactive compounds to enhance efficacy. Their incorporation into modern formulations for skin health demonstrates their versatility. For instance, topical preparations

containing ZnO-HM NPs have been developed for treating acne and eczema, leveraging their antioxidative and antimicrobial properties. Clinical trials have shown significant reductions in acne lesions and improvements in skin texture, highlighting their potential in dermatological applications [10].

Beyond their antimicrobial activity, ZnO-HM NPs exhibit strong antioxidant and anti-inflammatory properties that are directly relevant to wound healing. By reducing oxidative stress and modulating inflammatory signaling, these nanoparticles support fibroblast activity, angiogenesis, and epithelial regeneration, which are essential for effective tissue repair. Such multifunctional behavior highlights their potential as topical therapeutic agents for managing chronic and infected wounds [12].

The broad spectrum of biological activities exhibited by ZnO-HM NPs, including antioxidative, antimicrobial, and anti-inflammatory properties, makes them a highly versatile compound with numerous applications in medicine. The growing interest in natural products and the demand for effective, safe, and sustainable therapeutic agents underscore the need for further research into the potential of ZnO-HM NPs. As our understanding of their mechanisms deepens, ZnO-HM NPs are poised to play a significant role in developing novel treatments for a wide range of health conditions, from chronic inflammatory diseases to neurodegenerative disorders and skin health. The continued exploration of their applications in both traditional and modern medicine holds promise for advancing natural therapeutic strategies that meet the increasing demand for natural health products [13]. This study aims to rigorously investigate the enhanced combined efficacy of ZnO-HM NPs on wound healing through a combination of *in vitro* assays and zebrafish model studies, ultimately contributing valuable insights into their efficacy and potential clinical applications.

Materials and Methods

Preparation of ZnO-HM NPs

ZnO-HM NPs were synthesized by dissolving 2.2 g of zinc acetate dihydrate ($\text{Zn}(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$) in 100 mL of deionized water to prepare a 0.1 M solution. Simultaneously, 4 g of sodium hydroxide (NaOH) was dissolved in 100 mL of deionized water to prepare another 0.1 M solution. Hamamelitannin (1 mg/mL) was used as a bioactive surface-functionalizing and stabilizing ligand. ZnO nanoparticle formation occurred via alkaline precipitation, followed by phytochemical surface modification. The mixture was heated until a white precipitate forms, indicating the formation of the nanoparticles. After cooling, the precipitate was collected via centrifugation and washed with ethanol and deionized water to eliminate impurities. The resulting ZnO-HM NPs are dried and characterized through various techniques. Fourier Transform Infrared Spectroscopy (FTIR) analysis is conducted by preparing a pellet of the nanoparticles for examination using an FTIR spectrometer. X-ray Diffraction (XRD) analysis is performed on a powdered sample of the nanoparticles. Finally, UV analysis involves dispersing the nanoparticles in ethanol and measuring the absorbance spectrum using a UV-Vis spectrophotometer [14].

In vitro anti-inflammatory and antioxidant analysis

Albumin inhibition assay

To assess 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. Simultaneously, the synthesized ZnO-HM NPs were dispersed in an appropriate solvent to obtain the desired concentration. Test solutions of anti-inflammatory agents were then prepared 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 combined and incubated at a controlled temperature, such as 37°C, for a predetermined duration of one hour. A separate set of HSA tubes was subjected to the same incubation conditions without the nanoparticles to serve as a positive control for denaturation. After the incubation period, the samples were allowed to cool and then exposed to heat stress

by heating at 70°C for 20 minutes. Following this, the absorbance of each sample was measured at 660 nm using a UV-Vis spectrophotometer. A reduction in absorbance in the samples containing ZnO-HM NPs, compared to the control, indicated inhibition of albumin denaturation, suggesting potential anti-inflammatory properties of the nanoparticles [15].

Hydroxyl radical scavenging assay

A reaction mixture was prepared consisting of a hydroxyl radical source, Fenton's reagent (a 1:1 mixture of 10 mM FeSO₄ and 10 mM H₂O₂ solutions), and different concentrations of ZnO-HM NPs. The reaction mixture was incubated at room temperature. Salicylic acid was added to initiate the reaction between the hydroxyl radicals and salicylic acid, resulting in the formation of 2,3-dihydroxybenzoic acid. After incubation, the reaction was stopped by adding trichloroacetic acid (TCA), and thiobarbituric acid (TBA) was introduced to develop a pink chromogen. The tubes were heated, allowed to cool, and then centrifuged. Finally, the absorbance of the supernatant was measured at a wavelength of 532 nm using a UV-Vis spectrophotometer to assess the reaction's progress [16].

Minimum inhibitory concentration

Cultured each pathogen - *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus* - separately in appropriate growth media until they reached mid-log phase. Diluted the cultures to obtain a standardized bacterial suspension of about 5 × 10⁶ CFU/mL. Prepared a series of dilutions of the ZnO-HM NPs stock solution in the respective growth media to cover a range of concentrations. In a 96-well microplate, dispensed aliquots of the bacterial suspension into each well, followed by adding different concentrations of ZnO-HM NPs. Amoxicillin and an untreated control were included as positive and negative controls, respectively. Incubated the microplate at the appropriate temperature 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, assessed bacterial growth 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 ZnO-HM NPs at which no visible growth or significant decrease in optical density was observed compared to the control [17].

Zone of inhibition

In the well diffusion method, agar plates were prepared by pouring molten agar containing 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*. After solidification, bacterial suspensions of 5 × 10⁶ CFU/mL were spread evenly on the surface of the agar plates using a sterile swab. Wells were then created in the agar using a sterile cork borer, and different concentrations of the ZnO-HM NPs solution were added to the wells. Positive control (Amoxicillin) and an untreated control were also included. The plates were incubated at room temperature, and after incubation, the zones of inhibition around the ZnO-HM NPs treated wells were measured in millimeters (mm) using a calibrated ruler.

Ligand and receptor interaction studies

The experimental procedure involved the initial retrieval of 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 utilized to prepare the receptor structures by removing water molecules and non-essential ligands. The 3D structure of the ZnO-HM NPs was obtained from relevant literature and converted into suitable formats using Open Babel GUI Ver 2.0. AutoDock VER 1.5.7 was employed for molecular docking studies to predict binding interactions between ZnO-HM NPs and the receptors. Docking parameters were set, and binding affinity was evaluated by analyzing the docking results, including binding energy and interaction patterns. Finally, Discovery Studio Visualizer software was used to visualize the 3D and 2D binding interactions between ZnO-HM NPs and the receptor proteins [18].

In vivo studies

Zebrafish toxicity

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 acclimatization, the zebrafish were housed in 10 L glass tanks filled with dechlorinated water, equipped with aeration and filtration systems. Following a one-week acclimatization period to ensure physiological adjustment, the zebrafish were randomly divided into experimental groups, each consisting of 6 individuals to facilitate adequate statistical analysis. The experimental groups were exposed to varying concentrations of ZnO-HM NPs, ranging from 80 µg/mL to 160 µg/mL. Throughout the one-week exposure period, the survival rates of the zebrafish were monitored daily, calculated as the percentage of surviving zebrafish relative to the total number in each group at the start of the experiment [19].

Zebrafish wound closure experiments

In the *in vivo* wound healing experiment, zebrafish (n=6/group) were distributed into four groups: a control group, wounded zebrafish, and two experimental groups treated with ZnO-HM NPs at concentrations of 80 µg/mL and 160 µg/mL, respectively. The fish were anesthetized by immersion in a solution of 0.2% Tricaine methane sulfonate before being wounded with a sterilized scalpel behind the gill region, near the lateral line. Humane endpoints included ≥ 20% weight loss, abnormal swimming, loss of equilibrium, excessive hemorrhage, and impaired feeding. Fish were monitored twice daily. Every third day, the ZnO-HM NPs were administered to the wounded zebrafish, and the healing process was monitored with daily photographs. Zebrafish were anesthetized at specific intervals (0-, 7-, and 14-days post-injury), and the wounded sites were photographed and assessed for closure using ImageJ software. Wound healing progress was evaluated by periodically examining the wound area, with injured locations identified by observing differences in skin color between affected and unaffected regions. Healing progression was tracked until the wounded area fully regenerated and returned to its original coloration, indicating the completion of the healing process [19].

Table 1: Primers used for gene expression

Primers used for gene expression Gene	Forward primer (5'-3')	Reverse primer (5'-3')	Accession number
<i>MMP13</i>	GAGAAGGTTTGGGCTCTC TATG	TGAGTTGCTGTCTTCCTT GTAG	AF506756
<i>TNF-α</i>	AGAAGGAGAGTTGCCTTT ACCGCT	AACACCCTCCATACACC GCATTT	AF025305
<i>IL-1β</i>	TCAAACCCCAATCCACAGA G	TCACCTCAGCTCTTGGA TG	AY340959.1
<i>β actin</i>	AATCTTGCGGTATCCACG AGACCA	TCTCCTTCTGCATCCTGT CAGCAA	AF025305

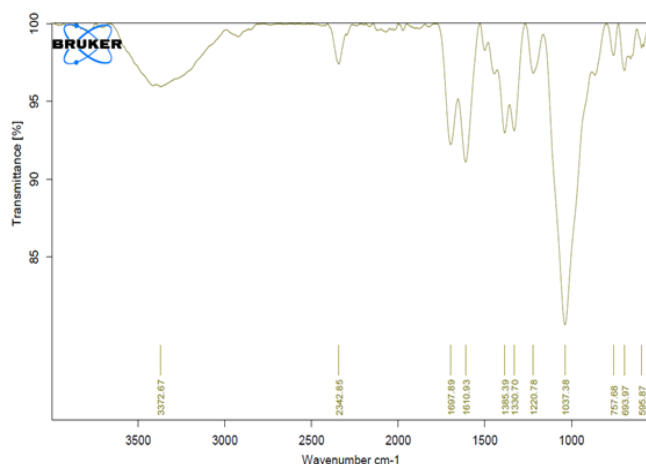


Figure 1: FTIR spectrum represent specific vibrational modes corresponding to functional groups present in the ZnO-HM NPs

Gene expression studies

Adult zebrafish were categorized into four groups: treatment 1 (ZnO-HM NPs at 80 µg/mL), treatment 2 (ZnO-HM NPs at 160 µg/mL), model (wounded zebrafish), and unwounded (control). Tissue samples from the wounded site were collected and stored at -80°C. The pooled wound tissue underwent homogenization (Polytron PT 1200E, Kinematic, Switzerland) for RNA isolation using TRIzol reagent (Invitrogen, Carlsbad, CA, USA). RNA concentration was determined using a NanoDrop One, followed by cDNA synthesis with 2.5 µg of 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 use. The primers used in this study are detailed in table 1, with zebrafish β -actin serving as the housekeeping gene. Quantitative real-time PCR (qRT-PCR) was conducted using a Thermal Cycler Dice Real-Time System (TaKaRa®) following a previously published protocol with slight modifications. Briefly, each qRT-PCR reaction consisted of 3 µL of cDNA template, 1 µL (10 µM) of each forward and reverse primer, and 5 µL of TB Green Premix Ex Taq II (TaKaRa®) qPCR mix. Primer specificity was verified 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 [20].

Statistical analysis

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

Results

Characterization of ZnO-HM NPs

The characterization results indicate that the ZnO-HM NPs possess distinct structural and chemical properties. FTIR analysis identifies characteristic peaks at wave numbers 3372.67, 2342.85, 1697.89, 1330.70, and 1037.38 indicating the presence of functional groups associated with both Hamamelitannin and zinc oxide (figure 1). These peaks correspond to various chemical bonds and molecular vibrations, providing insight into the composition and bonding within the ZnO-HM NPs. The relatively high amorphous fraction is attributed to dense organic surface coating by hamamelitannin, which may mask ZnO crystalline domains.

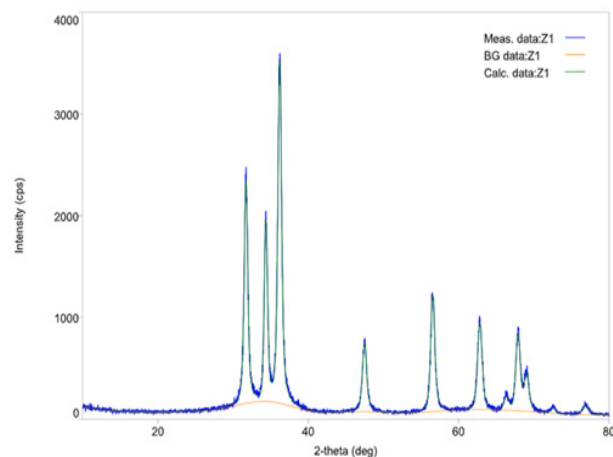


Figure 2: XRD analysis of ZnO-HM NPs illustrating the presence of a crystalline phase and amorphous phase

Average crystallite size was calculated using the Scherrer equation, confirming the presence of nanoscale ZnO crystallites consistent with the observed XRD peak broadening (figure 2). UV-Vis spectroscopy revealed an absorption peak at 268 nm, corresponding primarily to hamamelitannin surface functionalization, while ZnO core formation was confirmed by XRD and FTIR analyses (figure 3).

Inhibition of albumin denaturation and free radical scavenging activity

The results of the study on ZnO-HM NPs indicate promising properties in combating protein denaturation and oxidative stress. In the albumin denaturation experiment, ZnO-HM NPs at the higher concentration of 160 µg/mL exhibited 63% activity, which is slightly lower than the positive control, Ibuprofen, showing 72% activity. This suggests that ZnO-HM NPs effectively prevent protein denaturation in a manner similar to diclofenac. Similarly, in the hydroxyl radical scavenging assay, ZnO-HM NPs at 160 µg/mL demonstrated 69% activity, comparable to the positive control, ascorbic acid, which exhibited 75% activity. These results indicate that ZnO-HM NPs possess significant antioxidant capabilities, effectively neutralizing harmful hydroxyl radicals. Overall, these

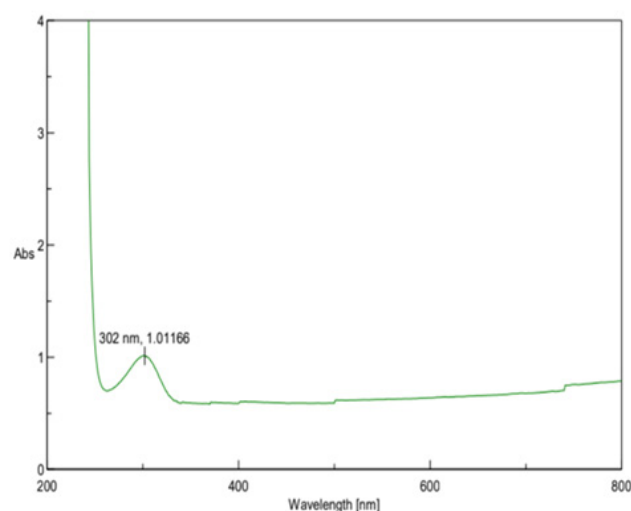


Figure 3: UV-Vis spectrum of synthesized ZnO-HM NPs

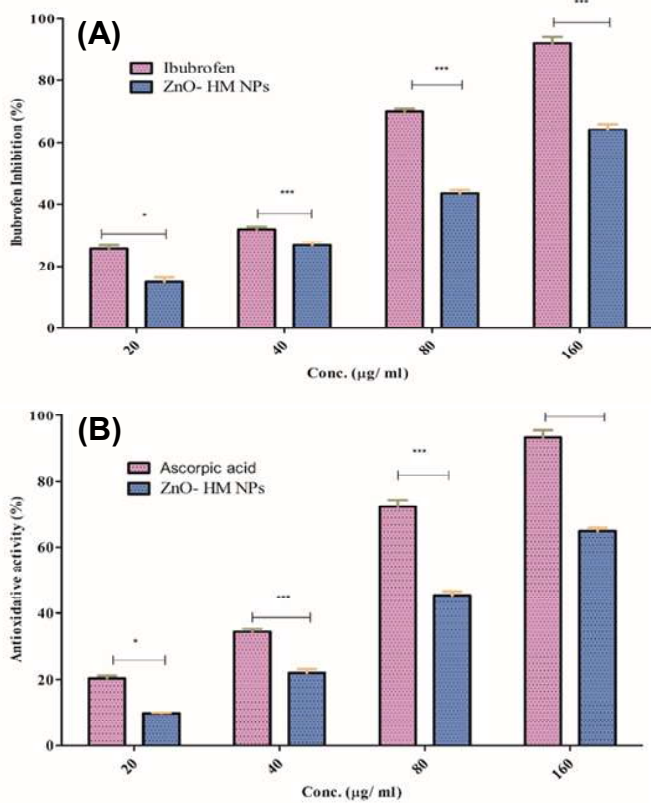


Figure 4: (A) Albumin denaturation Inhibition and (B) Hydroxyl radical scavenging activity of ZnO-HM NPs at different concentrations (20 µg/mL, 40 µg/mL, 80 µg/mL, and 160 µg/mL). Diclofenac and Trolox was used as a positive control. The *** represented the level of significance ($p < 0.05$) when the results were compared to the control. Data were presented as mean $\pm$ SD of three independent experiments

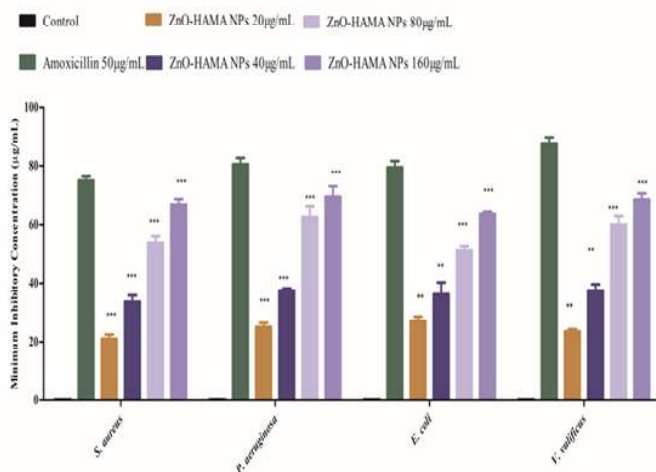


Figure 5: MIC of ZnO-HM NPs at different concentration against dental pathogens of *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus*. Amoxicillin was used as positive control. The *** represented the level of significance ($p < 0.05$) when the results were compared to the control. Data were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

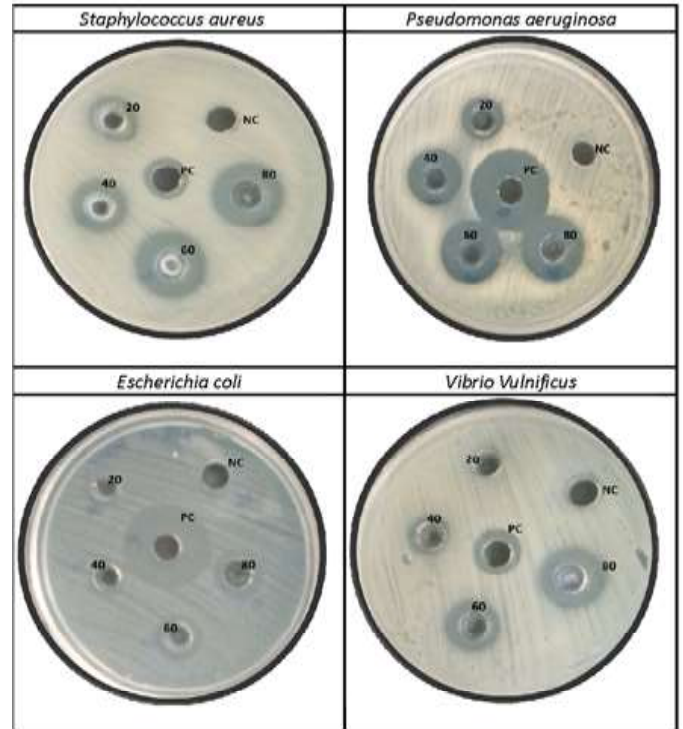


Figure 6: Zone of inhibition of different dental pathogen by ZnO-HM NPs. A – Control, B – Amoxicillin (50 µg/mL), at 80 µg/mL, and D - ZnO-HM NPs at 160 µg/mL. Zone of inhibition measured at mm

Table 2: Zone of inhibition (mm)

Bacterial Strain	Control (mm)	Amoxicillin (50µg/ml)	ZnO-HM NPs (80µg/ml)	ZnO-HM NPs (160µg/ml)
<i>Staphylococcus aureus</i>	11	10	7	8
<i>Pseudomonas aeruginosa</i>	14	8	6	10
<i>Escherichia coli</i>	15	6	4	5
<i>Vibrio vulnificus</i>	12	5	8	7

findings suggest that ZnO-HM 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 ZnO-HM NPs demonstrated their effectiveness against a range of pathogenic bacteria, including *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus*. The MIC values remained consistent at 80 µg/mL for all tested bacteria, indicating that concentrations at or above this level significantly ($p < 0.05$) inhibited their growth (figure 5). This highlights the broad-spectrum antimicrobial activity of ZnO-HM NPs across both Gram-positive and Gram-negative bacteria. Additionally, the zone of inhibition assay confirmed the antimicrobial potential of ZnO-HM NPs. At 80 µg/mL, ZnO-HM NPs produced zones of inhibition measuring 7, 6, 4, and 8 mm against *S. aureus*, *P. aeruginosa*, *E. coli*, and *V. vulnificus*, respectively (table 2). Increasing the concentration to 160 µg/mL resulted in larger zones of inhibition (8, 10, 5, and 7 mm), indicating a dose-dependent response. Notably, the zones of inhibition were greater compared to the positive control, amoxicillin (50 µg/mL). At 80 µg/mL, the antimicrobial activity of ZnO-HM NPs significantly improved, surpassing that of amoxicillin against all tested pathogens (figure 6).

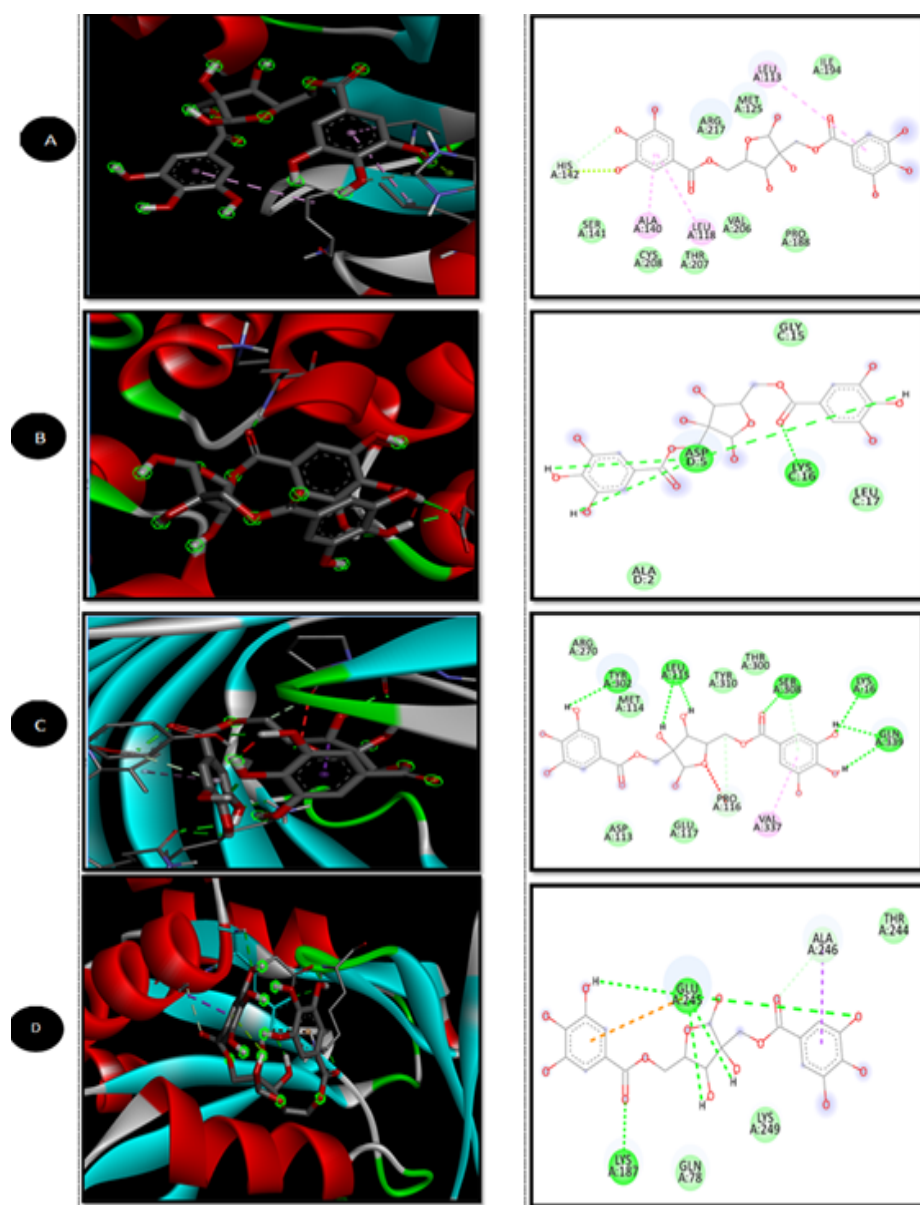


Figure 7: 3D and 2D interaction images of HM and wound-infecting bacterial pathogens. (A) 7S53 (antimicrobial protein), (B) 4NG2 (oxidative stress regulator), (C) 20MF (inflammatory mediator), (D) 5TV2 (wound healing protein). The interaction is observed with amino acids such as ALA (Alanine), LEU (Leucine),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

Table 3: Amino acid and Binding affinity value of the vanillic acid interaction with different dental pathogen receptors. as ALA (Alanine), LEU (Leucine), HIS (Histidine), ASP (Aspartic acid), LYS (Lysine), TYR (Tyrosin), VAL (Valine), GLN (Glutamine), ALA (Alanine), ARG (Arginine), GLU (Glutamic acid)

Receptor (PDB ID)	Ligand	Binding affinity (kcal/mol)	Amino acid interaction
<i>S. aureus</i> : Sortase A-substrate Complex (SrtA) (PDB: 7S53)	Hamamelitannin	-4.2	ALA, LEU, HIS
<i>P. aeruginosa</i> : LasR (PDB: 4NG2)	Hamamelitannin	-3.6	ASP, LYS
<i>E. coli</i> : Outer membrane porin (integral membrane protein porin) (PDB: 2OMF)	Hamamelitannin	-6.5	TYR, LEU, VAL, LYS, GLN
<i>V. vulnificus</i> : Nuclear Protein (PDB: 5TV2)	Hamamelitannin	-2.4	ALA, LYS, GLU

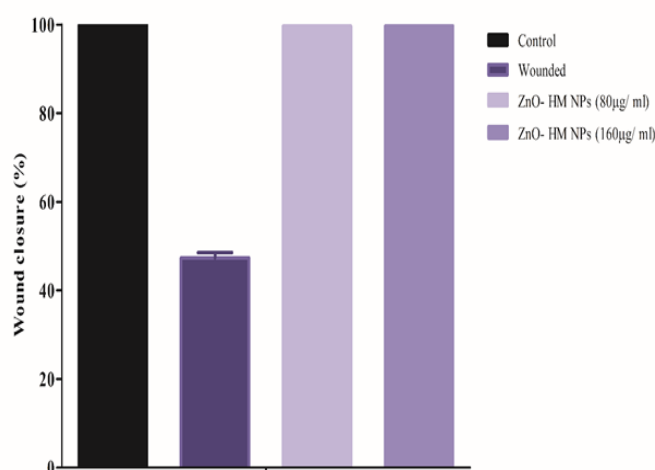


Figure 8: The survival rate analysis of zebrafish with different groups of control, wounded zebrafish, and exposure to ZnO-HM NPs (80 µg/mL and 160 µg/mL). The independent three experimental data were expressed as mean $\pm$ SD (n=6/group). The significant difference at $p < 0.05$ was expressed as *

Binding interaction with pathogenic receptor

The docking studies between ZnO-HM NPs and wound-infecting bacterial pathogens revealed varying binding affinities. *E. coli* exhibited the highest affinity (-6.3 kcal/mol), indicating a strong potential for ZnO-HM NPs to combat *E. coli* infections. The interactions involving amino acids such as LEU, PRO, HIS, and TYR likely contribute to this robust

binding. *S. aureus* followed closely with a slightly lower affinity (-5.5 kcal/mol), suggesting significant interactions and potential efficacy against this pathogen. In contrast, *P. aeruginosa* and *V. vulnificus* demonstrated lower affinities (-3.1 kcal/mol and -2.8 kcal/mol, respectively), indicating weaker interactions (table 3). These findings suggest that ZnO-HM NPs could be particularly effective against *E. coli* and potentially against *S. aureus* infections, as supported by the observed binding affinities and amino acid interactions (figure 7).

Survival rate analysis in zebrafish

The toxicity of ZnO-HM NPs was evaluated in adult zebrafish by comparing four groups: unwounded controls, wounded zebrafish, and wounded zebrafish treated with ZnO-HM NPs at 80 µg/mL and 160 µg/mL. The wounded untreated group exhibited reduced survival relative to unwounded controls, reflecting physiological stress associated with injury. In contrast, zebrafish treated with ZnO-HM NPs at both concentrations showed survival rates comparable to the control group, indicating no observable nanoparticle-induced toxicity. These findings suggest that ZnO-HM NPs are well tolerated within the tested dose range and do not elicit significant systemic toxicity in the zebrafish model. (figure 8).

Wound healing activity

The wound healing activity of ZnO-HM NPs was investigated on wounded zebrafish, focusing on concentrations of 80 µg/mL and 160 µg/mL over a period of 7- and 14-days post-wounding (dpw). Notably, treatment with ZnO-HM NPs at 80 µg/mL resulted in a 54% closure of wounds at 7 dpw, while at 160 µg/mL, the closure significantly ($p < 0.05$) increased to 62%. Remarkably, by 14 dpw, the closure rates further improved to 70% and 93% for the 80 µg/mL and 160 µg/mL concentrations, respectively, compared to the control group. These findings underscore the potential efficacy of ZnO-HM NPs in promoting accelerated wound closure in zebrafish models, suggesting their promise for further exploration in wound healing applications (figure 9).

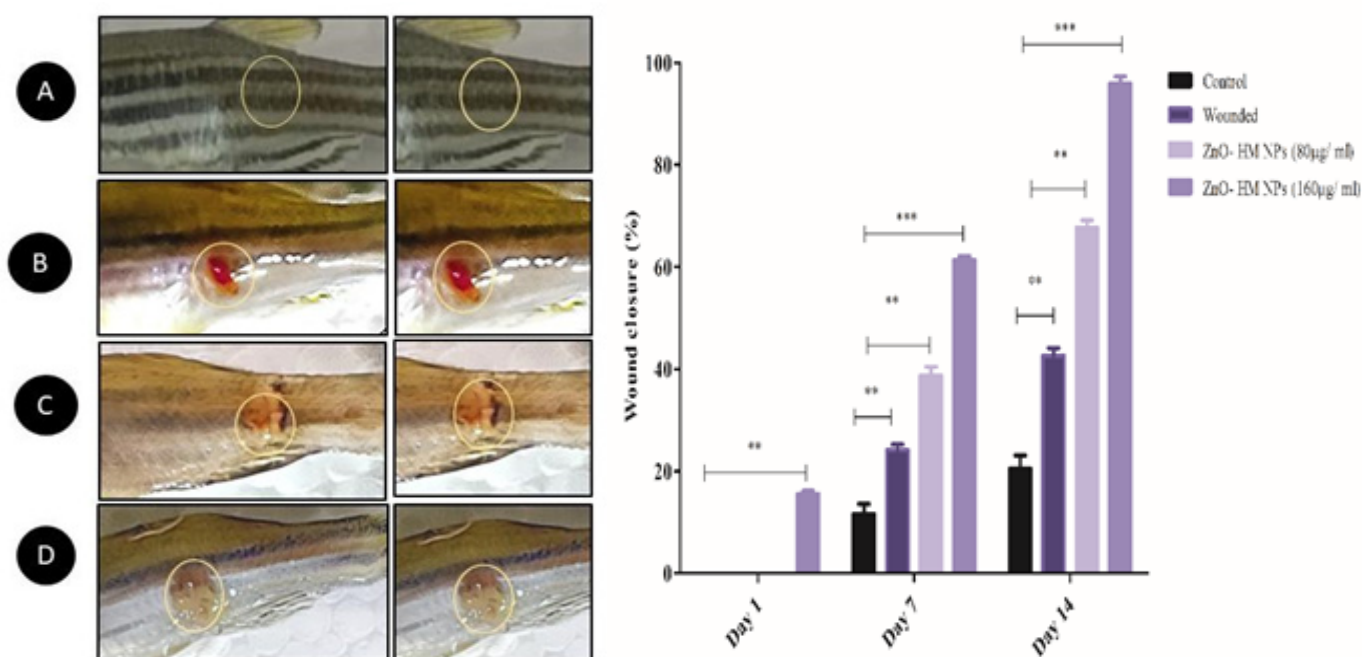


Figure 9: (A – D) Representative photograph of wounded zebrafish treated with ZnO-HM NPs at different concentrations. (E) The graphical presentation of the wound closure was measured using Image J software. The independent three experimental data were expressed as mean $\pm$ SD (n=6/group). The significant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

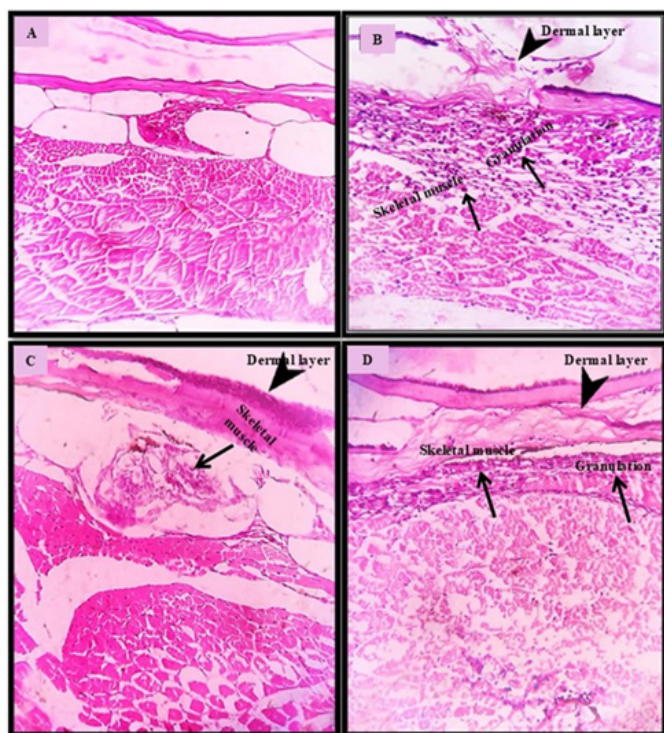


Figure 10: Histological analysis of wounded zebrafish tissue. (A) Control (unwounded zebrafish), (B) Wounded Zebrafish, (C) ZnO-HM NPs treatment at 80 µg/mL, and (D) ZnO-HM NPs treatment at 160 µg/mL. The tissue layers include skeletal muscle, dermal layer, granulation tissue, and epithelial layer with immune cell infiltration

Wound morphological analysis

Histological analysis of wounded zebrafish tissue. (A) Control (unwounded zebrafish), (B) Wounded Zebrafish, (C) ZnO-HM NPs treatment at 80 µg/mL, and (D) ZnO-HM NPs treatment at 160 µg/mL. The tissue layers include skeletal muscle, dermal layer, granulation tissue, and epithelial layer with immune cell infiltration. The microscopic examination of zebrafish treated with ZnO-HM NPs, compared to the untreated control group, revealed distinct differences in tissue composition. The treated group displayed a densely layered epidermis, significant proliferation of granulation tissue, and clear formation of new blood vessels (neoangiogenesis). Notably, the treated zebrafish exhibited 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 the ZnO-HM 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 ZnO-HM NPs treatment in wound healing, the gene expression levels of matrix metalloproteinase 13 (MMP13) and pro-inflammatory cytokines such as TNF-α and IL-1β were evaluated. The higher concentration of ZnO-HM NPs at 160 µg/mL was selected for further gene expression studies due to its ob-

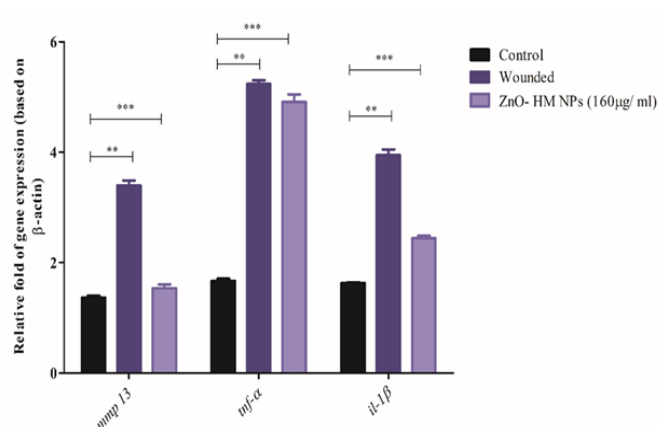


Figure 11: Effect of ZnO-HM NPs treatment group on the mRNA expression level of MMP13, TNF-α, IL-1β. Data were expressed as mean + SD of three independent experiments. * $p < 0.05$ as compared to the control

served superior activity and lower toxicity. Wound tissues for gene expression analysis were collected at Day 14 post-injury, representing the resolution phase of healing. 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-1β (4.6-fold). In contrast, the expression levels of MMP13 (1.7-fold), TNF-α (3.4-fold), and IL-1β (2.3-fold) were significantly downregulated in the ZnO-HM NPs treated group (160 µg/mL).

Discussion

The emergence of ZnO-HM NPs as a novel therapeutic strategy in wound healing highlights the innovative integration of zinc oxide nanoparticles (ZnO NPs) with Hamamelitannin, leveraging their distinct biological activities to address the multifaceted challenges of wound management. ZnO NPs are renowned for their potent antibacterial properties, which are essential for preventing infections - a common and significant barrier to healing in chronic wounds. Their ability to reduce bacterial load is complemented by anti-inflammatory effects that help modulate the inflammatory response, thus minimizing delays in healing caused by excessive inflammation. Additionally, their antioxidant capabilities play a critical role in countering oxidative stress, which can adversely affect cellular health and impede recovery [21]. When combined with Hamamelitannin, a natural polyphenolic compound recognized for its wide range of biological activities, the wound healing potential is further enhanced. Hamamelitannin not only offers antioxidative, antimicrobial, and anti-inflammatory benefits but also effectively scavenges free radicals, mitigating oxidative damage. This enhanced combined efficacy between ZnO NPs and Hamamelitannin presents a promising avenue for advancing wound healing therapies, addressing both infection control and the promotion of tissue regeneration. In this discussion, we will explore the implications of these findings and the potential of ZnO-HM NPs in clinical applications for improved wound care. Characterization of Zn-HM NPs reveals crucial structural and chemical properties essential for potential wound healing applications. In this study, the promising antioxidant and anti-inflammatory therapeutic potential of ZnO-HM NPs in wound healing can be attributed to their ability to stabilize proteins and scavenge harmful oxidative agents [22]. By preventing protein denaturation, these NPs help maintain cellular integrity in the wound environment, reducing inflammation similarly to established anti-inflammatories like diclofenac. Their significant antioxidant activity also mitigates 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. Antimicrobial activity is crucial for effective wound healing, as it directly combats infection, one of the primary complications that can impede the healing process. Infections can slow 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. Recent studies have shown that electrospun membranes loaded with ZnO-HM NPs exhibited antibacterial activity against *E. coli* and *S. aureus*. In line with previous results, our study demonstrated that the minimum inhibitory concentration (MIC) and zone of inhibition assays highlighted the broad-spectrum antimicrobial activity of ZnO-HM NPs, suggesting their significant utility in wound healing applications. 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 superior antimicrobial performance of ZnO-HM NPs compared with amoxicillin can be attributed to fundamentally different mechanisms of action. While β -lactam antibiotics primarily inhibit bacterial cell wall synthesis, ZnO-based nanostructures exert multi-modal antimicrobial effects including reactive oxygen species (ROS) generation, membrane lipid peroxidation, protein oxidation, and intracellular DNA damage. The nanoscale dimensions of ZnO facilitate close contact with bacterial membranes, promoting electron transfer and localized ROS production such as hydroxyl radicals and superoxide anions. This oxidative species compromise membrane integrity, increase permeability, and ultimately induce bacterial apoptosis-like death. Furthermore, hamamelitannin surface functionalization may enhance bacterial adhesion and local ROS concentration while simultaneously interfering with quorum-sensing pathways, thereby suppressing biofilm maturation. This dual physical-chemical mechanism explains the ability of ZnO-HM NPs to overcome conventional resistance pathways and provides a rationale for their enhanced antimicrobial efficacy observed in this study [23].

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 [24].

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 [25].

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

In this study, HA, 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, ZnO-HM NPs hold potential for enhancing wound healing and reducing infection risk, particularly in high-risk populations or clinical settings where infection control is critical [26].

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 nanoemulsions with *Elaeis guineensis* leaf extract in zebrafish models, observing effective wound closure after treatment [27]. Similarly, our study's results regarding the toxicity analysis and wound healing activity of ZnO-HM 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 $\mu\text{g}/\text{mL}$, underscores the favorable safety profile of ZnO-HM NPs. This finding is particularly promising, suggesting that these nanoparticles may be well-tolerated in biological systems, a crucial consideration for any therapeutic intervention.

Additionally, the remarkable wound healing activity observed with ZnO-HM NPs highlights their potential as effective wound healing agents. Concentrations of 40 $\mu\text{g}/\text{mL}$ and 80 $\mu\text{g}/\text{mL}$ 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. Furthermore, 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 ZnO-HM NPs promote tissue regeneration and repair, potentially enhancing the overall wound healing process. These findings open exciting possibilities for developing ZnO-HM NPs-based wound dressings or topical formulations for clinical use [28].

MMP13 plays a dual role during wound healing, contributing initially to extracellular matrix remodeling while excessive or prolonged expression leads to pathological tissue degradation. In the present study, wounded zebrafish exhibited elevated MMP13 expression, reflecting the active inflammatory and remodeling phase. ZnO-HM NP treatment resulted in moderated MMP13 levels by Day 14 post-injury, indicating controlled matrix remodeling rather than suppression. This suggests that the nanocomposite supports physiological tissue regeneration while preventing excessive proteolytic damage, a balance critical for successful wound resolution. MMP13 facilitates tissue remodelling by degrading extracellular matrix components, while pro-inflammatory cytokines like TNF- α and IL-1 β initiate and amplify the inflammatory response crucial for wound healing. 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 [29].

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 ZnO-HM 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 ZnO-HM NPs in wound management by regulating inflammatory signalling pathways and promoting tissue repair.

This study has several limitations. Individual ZnO-only and hamamelitannin-only controls were not included across all assays; therefore, the observed outcomes are described as enhanced combined efficacy rather than true combinations. UV-Vis spectroscopy primarily reflects ligand functionalization, while nanoparticle morphology was inferred from XRD without SEM or TEM validation. Molecular docking was performed using hamamelitannin alone due to current limitations in modeling inorganic nanostructures. Future studies will incorporate factorial designs, ultrastructural characterization, and mammalian wound models to further validate translational relevance.

Conclusion

In conclusion, the study highlights the significant potential of ZnO-HM NPs in enhancing wound healing through their antioxidant, anti-inflammatory, and antimicrobial properties. Their favourable safety profile in zebrafish suggests good biocompatibility, making them promising candidates for therapeutic applications. The accelerated wound closure and improved tissue repair indicate their efficacy in promoting regeneration while regulating inflammatory signalling pathways. Additionally, their broad-spectrum antimicrobial activity against common pathogens enhances their role in preventing infections during healing. These findings support the development of ZnO-HM NPs-based topical formulations and wound dressings to improve patient outcomes in clinical settings. Future research should focus on optimizing these formulations and exploring the underlying mechanisms of their therapeutic effects, potentially leading to innovative solutions for effective wound care.

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