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In vitro chronic wound healing using collagen and plant extract along with zinc nanoparticles

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Abstract

INTRODUCTION: While the use of zinc nanoparticles (ZnNPs) as an antibacterial agent in the biomedical industry has recently attracted significant attention, collagen has aroused significant interest as a biomaterial in medical and tissue engineering applications.
OBJECTIVES: In order to create biofilm loaded with biosynthesized ZnNPs for use in chronic wound healing applications, type-I collagen was extracted from the study's subject. by the acid soluble collagen technique, collagen was isolated from the fish skin of the trevally and identified by SDS-PAGE. Aqueous extract from Cassia fistula leaves was also used to greenly manufacture stable ZnNPs, which were then characterized by UV-Vis, FTIR, and XRD measurements.
METHODS: Collagen and ZnNPs were then added to polyvinyl alcohol (PVA), creating a thin biofilm that had a high biocompatibility due to the production method's absence of a chemical reducer and crosslinking agent. When tested against the harmful bacteria, both ZnNPs alone and PVA/Collagen/ZnNPs biofilms showed potent antibacterial activity.
RESULTS: By using the MTT test, the cytotoxic effects of collagen and ZnNPs on the Vero cell line were evaluated. With 97.76% wound closure, the PVA/Collagen/ZnNPs biofilm demonstrated strong in vitro wound scratch healing efficacy.
CONCLUSION: The findings show that the PVA/Collagen/ZnNPs film dramatically increased cell migration by 40.0% at 24 hours, 79.20% at 48 hours, and 97.76% at 74 hours.

Keywords: Type-I collagen, Cassia fistula, Zinc nanoparticles, Anti-Bacterial culture, MTT assay, Biofilm

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1. Introduction

In connective tissue, which is found in cartilage, bones, tendons, ligaments, and skin, collagen serves as an adhesive. It is crucial for sustaining physical health and makes up more than one-third of the protein content. Fibroblasts are the main producers of collagen. The shape and structural properties of a collagen molecule are controlled by its triple helical domain.
An essential component of wound healing is the extracellular matrix protein collagen, which provides a surface for inflammatory cytokines and other growth factors at the site of damage. Collagen has been used as an extra wound treatment to speed up the healing process since it plays a crucial role in modulating a number of these processes.

Plant extracts and natural medicine products are often used to treat wounds. Phytochemicals are useful for treating a range of ailments and have chemopreventive properties. The biological reactions govern the healing of wounds. Superoxide anion radicals are created during the inflammatory stage to get rid of microorganisms at the wound site. Vascular endothelial growth factor (VEGF) is elevated by plant extracts rich in proanthocyanins, polyphenolic flavonoids, and polyphenols, which also encourage angiogenesis and blood flow. The leaf extracts possess a wide range of activity and propose its potential application in the management of infectious illnesses [3].

One of the most significant uses of nanomaterials in the healthcare industry is drug delivery. Zinc oxide nanoparticles (ZnO-NP) have been shown in several investigations to possess exceptional antibacterial capabilities against both gram-positive and gram-negative bacteria. The human body needs zinc since it is an active element with potent reducing capabilities. Strong antibacterial activity at low concentrations and affordability are only two benefits of ZnO nanoparticles. It will probably definitely take 15 to 20 minutes after ZnO NP exposure for the bacterial species' cytoplasm membrane to be affected. The chemical damaged the membranes of more than 70% of the cells [4]. Since persistent inflammation, increased metalloproteinases and other enzymes that break down extracellular matrix (ECM) components, and improper activation of soluble mediators in the wound healing process are major components of the difficult environment of a chronic wound, collagen plays a critical role in a number of biological processes regarding wound healing [6]. Further study aimed to synthesize Zn nanoparticles with leaf extract and test their antimicrobial effectiveness against certain microbes. [7].

The current study mainly focuses on extracting and characterizing type-I collagen from the skin of Trevally fish, combining it with biosynthesized ZnNPs, and developing biopolymer films to test their potential against gram-positive and gram-negative pathogens, as well as evaluating their in vitro cytotoxicity and wound healing efficacy [8]. The in vitro scratch assay is ideal for researching cell interactions' impact on migration, mimicking wound healing, and allowing live cell imaging during migration for monitoring intracellular events [11]. The composite films' surface morphology and structure are notably influenced by increased concentrations of the base component. Analyses using X-ray diffraction (XRD) and Fourier transform infrared spectrometry (FTIR) validate the structural interactions within the base component [12].

2. Methodology

The methodology is shown below in Figure 2.1

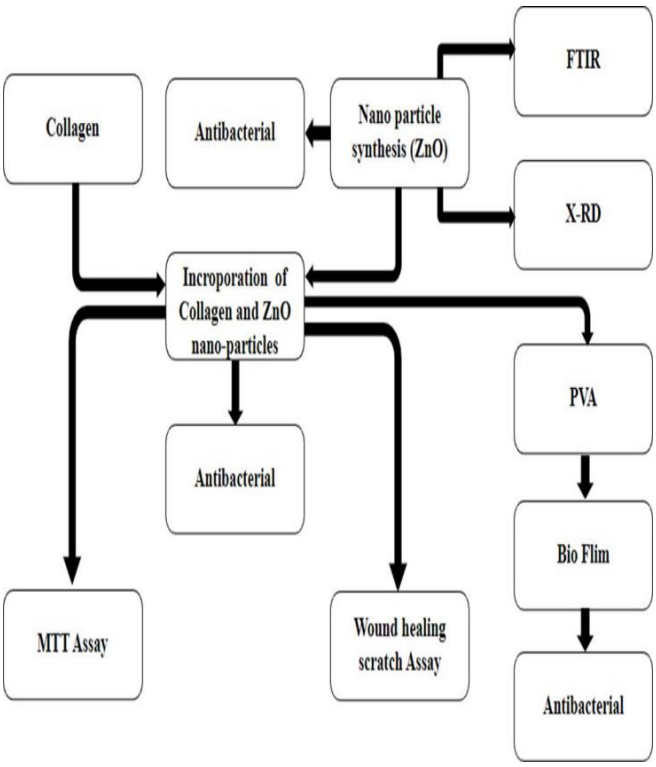

Figure 2.1 Block Diagram

2.1 Extraction of collagen

It was decided to use the skin of Trevally fish as the main source for the acetic acid technique of extracting Type-I collagen. Using double distilled water, a series of rigorous sterilizations were carried out to clean the fish skin. After that, the skin was cut into tiny, sterile pieces (0.5 x 0.5 cm), kept on ice at a low temperature, and collagen extraction was started [14].

Pretreatment: removing non collagenous tissue. Fish skin is first treated with a NaOH solution (1 gram of NaOH in 250 ml of DH2O), and then it is chilled. The resulting mixture is filtered before being blended with a freshly made solution of 0.8 mol/lit NaOH and being chilled. The final goal of this procedure is to remove non-collagenous proteins from the skin, and it is done every 24 hours for a total of 72 hours [15].

The fish skin is removed from the NaOH solution and mixed with an acetic acid solution (15 ml of acetic acid in 500 ml of distilled water). A total of 300 ml of the fish skin and acetic acid solution combination is homogenized before being subjected to two separate 30-minute periods of acetic acid digestion at 900 rpm. After that, the mixture is covered with aluminum foil and kept chilled at 4°C. For

two days, the homogenization procedure is carried out only once per day.

After being homogenized for 72 hours, fish samples were centrifuged in 8 tubes with a 35.5 level at 9000 rpm for 20 minutes at 4°C, yielding 400 ml of supernatant. The supernatant was mixed with 2 mol of NaCl for 30 minutes on a hot plate stirrer before being chilled for 24 hours. The pellets were discarded. Collagen samples that had been subjected to acid treatment were centrifuged once more, and the pellets were collected and dialyzed for three days at 4°C in a phosphate buffer solution [16].

After three days, the dialysis bag is removed and submerged in an acetic acid solution (2 ml of acetic acid in 500 ml of distilled water). Then, it is kept in a refrigerator at or below 4 degrees Celsius. The bag is taken out of the acetic acid solution after 48 hours and put in distilled water. For future investigation, the gathered collagen is kept in a freezer at 4°C.

2.2 Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) analysis

A charged molecule flows toward an electrode with an opposing charge in an electric field, according to the principle. The relative mobility of charged molecules is crucial for their separation. We used a 10% resolving gel and a 10% stacking gel in accordance with Piez et al.'s SDS-PAGE technique [17]. After that, we used Coomassie Blue R-250 to dye the final gel. We used a continuous current of 30 mA for 6 hours to separate the subunits. Finally, we used UV light to inspect the bands' positions on the gel to determine the subunits' molecular masses.

2.3 Plant extraction

The extraction of plant material is the first step in the current investigation, which is followed by an analysis of biological activity. The phytochemical characteristics of Cassia fistula led to its selection for the research. These plants' leaves were gathered from the Kollimalai Hills in Tamil Nadu, let to naturally dry in the sun, and then extracted using a decoction. The leaves were naturally dried after being cleaned with 50 cc of distilled water, combined with water, and cooked at 60 °C for one hour. The solution was filtered via Whatman filter paper and exhibited in hues of yellow, orangish red, and light brown. Later, further ZnO preparation was done using the extract solution [18].

Phytochemical analysis- For the treatment of wounds, plants offer antibacterial and antioxidant effects. They create terpenoids, alkaloids, and phenolic compounds, among other organic substances. These substances aid in the healing process and wound contraction [19].

2.4 Biosynthesis of Zinc nanoparticles

The zinc acetate solution was made by combining 21.94 grams of zinc acetate with 50 milliliters of water, then agitating the mixture for 20 minutes at 35 degrees Celsius. By mixing distilled water with 4 grams of NaOH powder for 3 minutes at 35 degrees Celsius, a NaOH solution was also made. The 10ml of leaf extract was added dropwise after the Zinc acetate and NaOH solutions had been combined.

To eliminate contaminants, the yellow liquid was thoroughly cleaned with distilled water and alcohol. Alkaloids, flavonoids, and phenols, which were present in high concentrations in the mixture throughout this process, were helpful in stabilizing and converting zinc salts into zinc oxide nanoparticles (ZnO NPs). These particular biological antioxidants have anionic radicals that make it easier to convert zinc salts into ZnO nanoparticles [20]. Additionally, the alkalinity of the combination encourages a strong interaction between the positively charged Zn2+ ions and OH ions, which enhances crystallization and leads to the production of tiny ZnO NPs.

2.5 Infusion of collagen with cassia fistula along with ZnNPs

Collagen from Trevally fish scales and Cassia fistula leaves extract were combined with zinc nanoparticles using a crosslinker. The collagen solution was prepared using 0.05 M acetic acid and agitated for 1 hour. It was then incubated for 24 hours at 4°C, filtered, and homogenized. The plant extract and ZnNPs were added to the collagen solution and stored for further analysis.

Antibacterial analysis of ZnO NPs incorporated collagen- In order to conduct the antibacterial test, the Agar well method was utilized with the amalgamation of collagen and ZnO nanoparticles incorporated into the solution, and the procedure was subsequently repeated. The observed outcomes were represented by the inhibition zones [21].

2.6 Preparation of PVA film – biofilm

The solution casting method was used to create a biofilm formed of polyvinyl alcohol (PVA) that contains collagen and ZnNP. A homogeneous solution was created by fully dissolving 8g of PVA in 100ml of double-distilled water while stirring constantly at room temperature. Collagen and ZnNPs were then gradually added and mixed for 40 minutes at a temperature of 30°C. The resulting slurry was then put to a mold and dried at 40°C for 24 hours to produce a thin layer. Then, a similar procedure was used to make the control film, but without the inclusion of zinc

nanoparticles. Films created using PVA, collagen, and ZnNPs were gathered for more research [22].

Antibacterial analysis of drug incorporated film and control- The antibacterial efficacy of the PVA/Collagen/ZnNPs biofilm was assessed using the disk diffusion technique (1940). Bacterial culture was consistently added to nutritive agar using sterilized cotton swabs. The PVA/Collagen/ZnNPs film was cleaned, as was the PVA film without collagen or ZnNPs. On the culture swabbed plates, the biofilm was put in 8 mm discs. The establishment of an inhibitory zone was investigated during an overnight incubation at room temperature [23].

In vitro cytotoxicity effect- In 96-well or 384-well plates with a final volume of 100 L/well or 25 L/well, respectively, cells are produced and subjected to test chemicals. A 37°C, 5% CO2 incubator is used for incubation for the predetermined amount of time, such as 24, 48, or 96 hours. Following incubation, 140 L for a 96-well plate and 35 L for a 384-well plate of MTT working solution are added to each well [24]. The mixture is then incubated for 1 to 4 hours at 37°C, shielded from light, with longer incubation durations potentially necessary depending on the cell type and concentration. To dissolve the formazan crystals, 100 L of a solubilization solution are added to each well, and thorough solubilization is accomplished by mixing. At 570 nm, absorbance is measured.

2.7 In vitro wound scratch activity

The current investigation was carried out in accordance with a set protocol [25]. On 6-well plates containing 8 105 cells each, vero cells were grown until they achieved 90% of their original size under ideal growth conditions. The wound was then subjected to a PVA/Collagen/ZnNPs film for 48 hours along with a concentration of 20 g/ml of the commercial medication Cetrimide, which acts as the positive control.

3. Results

3.1 Collagen extraction and SDS-PAGE analysis

SDS-PAGE analysis, which yielded a pattern compatible with normal type-I collagen, was used to verify the effective extraction of collagen from Trevally fish skin. Two thicker and two thinner bands are shown in the collagen electrophoretic pattern. There are several trimers of chains in the skin of trevally. The bands had molecular weights of 136 and 127 kDa, respectively, and the 1 band, which represents type I collagen, was twice as intense as the 2 band.

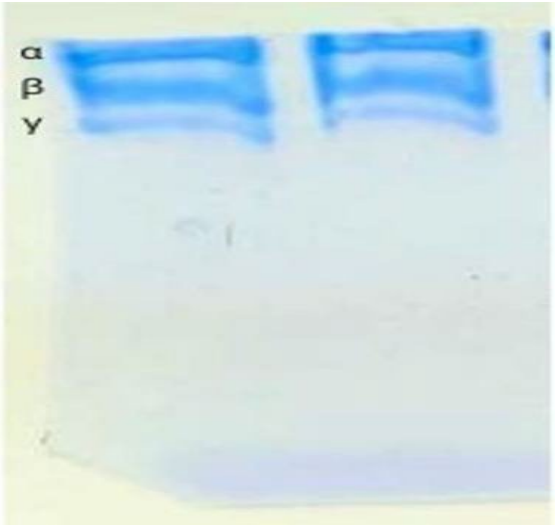

Figure 3.1 SDS-PAGE of collagen

3.2 Analysis of leaf extract

The three plants in question, namely Eclipta prostrata, Catharanthus roseus, and Cassia fistula, have undergone phytochemical analysis. Through conducting 10 tests to detect the presence of various metabolites such as steroids, phenolic compounds, alkaloids, carbohydrates, glycosides, saponins, amino acids, and phenolic compounds, it was possible to determine whether these substances are present in the three plant samples. The Figure 3.2 shows the resultof phytochemical analysis of the Cassia fistula extract. Based on the results obtained, it was found that the leaves of Cassia fistula were the most suitable choice.

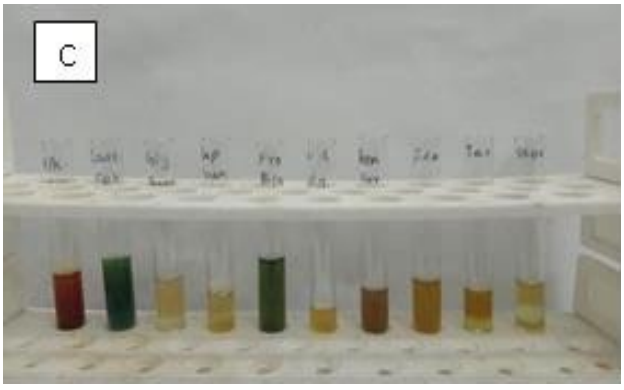

Figure 3.2 Result of phytochemical analysis (C-Cassia fistula)

This is due to the presence of steroids in Catharanthus roseus, which have been shown to inhibit tissue growth

and therefore used in cancer treatment to destroy cells. Additionally, amino acids are essential for wound healing, but areabsent in Eclipta prostrate. Thus, the analysis results were considered in the selection of Cassia fistula as the preferredplant sample.

3.3 UV-Visible spectroscopy

This method involves studying how the synthesized sample interacts with ultraviolet and visible light, providing important information about its optical properties and electronic structure. The absorption spectrum at room temperature of ZnOnanoparticles that were fabricated through biosynthesis is presented in this study. The absorption wavelengths of the nanoparticles fall within the boundary of the absorption spectrum of bulk ZnO, which is 200 to 400nm. The result of the UV-Vis spectroscopy of the Zinc nanoparticle is illustrated in Figure 3.3, where the absorption band at 390nm is attributed to ZnO nanoparticles.

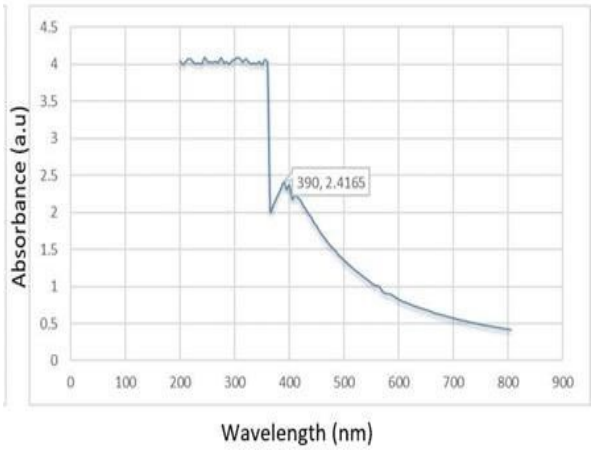

Figure 3.3 UV-Visible spectroscopy result of zinc nanoparticles

The slight alteration of the modification peak could be due to the differences found in the size and orientation of theparticles.

3.4 FTIR- Identification of the zinc oxide nanoparticle

The FTIR (Fourier transform infrared) spectroscopy is used as a confirmatory test to validate the presence of Zn nanoparticles. By analyzing how the sample interacts with infrared radiation, characteristic absorption bands can be identified that indicate the presence of Zn nanoparticles. FTIR was employed to identify and detect the peak of activecomponents in the powder, as well as newly formed compounds through bonding and stretching. The study utilized FTIR spectra, which were obtained using a Fourier transform and analyzed on a powdered sample of zinc oxide nanoparticles at room temperature and ambient humidity. The spectra were obtained approximately within the scope of 4000 - 400 cm-1, with a spectral resolution of 4 cm and averaged over 32 scans. FTIR Spectra studies, as shown in Figure 3.4, provided information on the chemical bonding between Zn and O, as well as the functional groups presentin the particles.

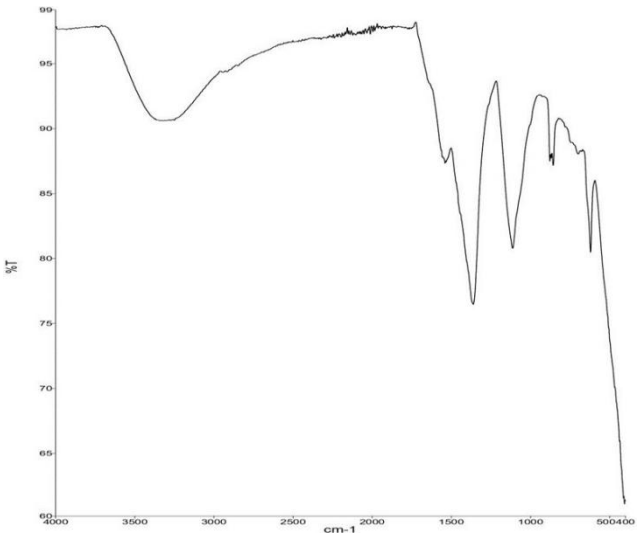

Figure 3.4 Result graph of FTIR for ZnO NPs

3.5 XRD X-RAY Diffraction analysis of Zinc nanoparticles

The hexagonal unit cell structure of ZnO nanoparticles was revealed through analysis of their XRD patterns. The existence of a definite line broadening in the peaks obtained from X-ray diffraction (XRD) suggested that the fabricated material consisted of particles within the nanoscale spectrum. The size, position, and range of the peaks, as well as the FWHM information, were obtained by examining the XRD findings shown in Figure 3.6.

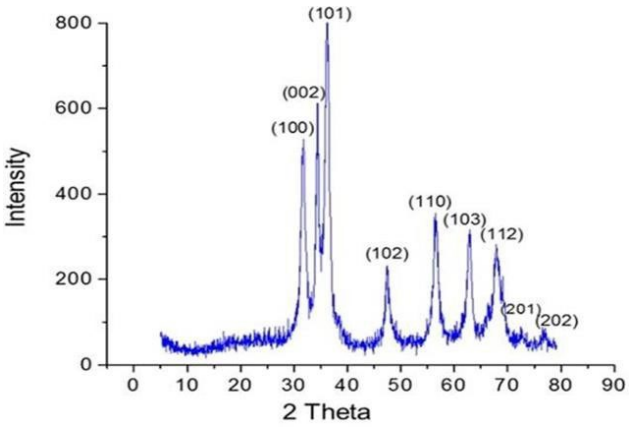

Figure 3.5 Reference XRD graph (Courtesy: researchgate.net)

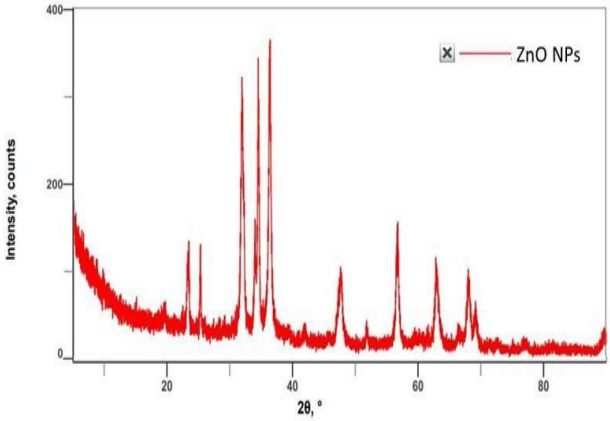

Figure 3.6 XRD result graph
Debye-Scherrer formula [33] was utilized to determine the diameter of the synthesized ZnO nanoparticles.

3.6 Antibacterial activity

Here the antimicrobial activity is done to ensure the quality of each component of the final product that is the biofilm.The antimicrobial properties of the zinc oxide nanoparticles, collagen and biofilm were tested against the gram-positivebacteria such as [Bacillus subtilis (BS), Staphylococcus aureus (SA)] and Gram- negative bacteria [Escherichia coli (EC), Pseudomonas aeruginos (PA)], which were purchased from the with the help of Avigen biotech lab through the dkdiffusion method.

Analysis of zinc oxide nanoparticles- The bacterial cells were subjected to incubation for 24 hours in a growth medium containing varying concentrations of ZnNps samples, specifically at 25%, 50%, 75%, and 100%. The antibacterial activity of the selected microorganisms, both gram-negative and gram-positive, was assessed based on the zones of inhibition. The results depict good sensitivity of the bacteria towards biosynthesized Zinc oxide nanoparticles, as shown in the numerical data presented in Table 1. The efficiency of the biosynthesized Zinc nanoparticles was determined by measuring thediameter of the clear zone, as evidenced in Figures 3.7 and 3.8. Furthermore, the antibacterial activity increases proportionally to the concentration of ZnNps, with 100%.

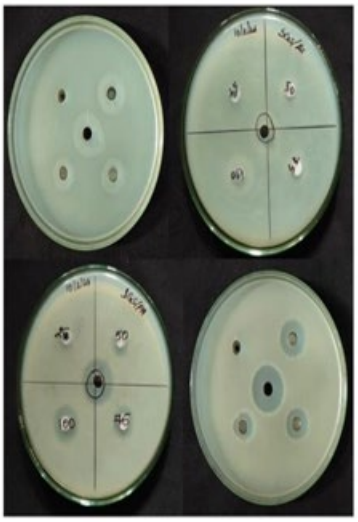

Figure 3.7 Antibacterial activity Bacillus subtilis and pseudomonas aeruginosa

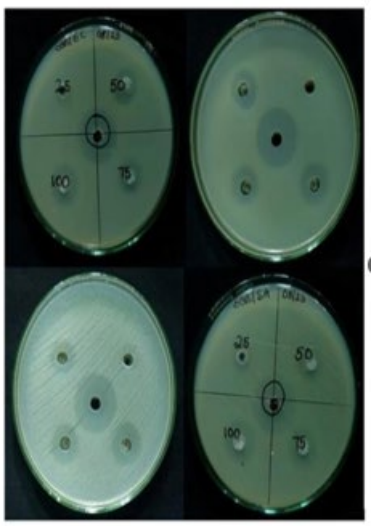

Figure 3.8 Antibacterial activity against Escherichia coli and Staphylococcus aureus

Using an inverted microscope, researchers evaluated the efficacy of zinc nanoparticle integrated collagen in wound healing and estimated the percentage of wound healing. The results showed that the wounds healed at a rate of 40% on the first day, approximately 79% on the second day, and reached a peak potency of 97% on the third day. Moreover, the healed wound cells appeared healthy. In comparison, the control group showed 77% wound healing on the third day. A comparison between the wound healing rate of the sample and the control group revealed a 20.76% faster healing rate. The pictorial representation of the in vitro scratch wound healing is shown in Figure 3.12 below, indicating that the combination of collagen fibre and zinc nanoparticles has a robust healing capability. Prior research has demonstrated the positive impacts of zinc nanoparticles on wound healing processes, specifically in terms of promoting cell migration and proliferation. These effects are essential in initiating the crucial proliferation phase of the healing process.

Unlike previous studies in this field, this paper consists of natural antibacterial potential of Cassia fistula by analysing its phytochemical properties. This helped us harness the biofilm's effectiveness in combating infections. Furthermore, the use of PVA in our biofilm application has contributed to a significant cost reduction, making it economically viable for wider clinical implementation. The study showcases a reduction in complications associated with collagen application through comprehensive cytotoxicity testing. Additionally, the final biofilm exhibits exceptional biocompatibility, as evidenced by in vitro testing.

Testing the PVA/Collagen/ZnNPs biofilm on diabetic rats in future research shows great potential. Diabetic rats provide a suitable model for studying chronic wounds, which resemble the slow healing wounds commonly found in diabetic patients. By examining how this biofilm performs in such a context, valuable insights can be gained. Subsequent studies could focus on parameters like wound healing speed, tissue regeneration, and the impact of the biofilm on diabetes related complications. This research direction offers to enhance our understanding of the therapeutic possibilities of biofilm for individuals suffering from diabetes.

The progress in computer processing has opened up possibilities for AI-based systems to improve diagnosis accuracy in different areas of health care. However, we can anticipate even greater advancements in the computational capabilities of wound care in the near future. These developments will assist with clinical diagnoses, evaluating potential treatment efficiency, and predicting outcomes. The machine learning algorithms have been used to analyse electronic health records (EHR) data and predict how long it may take chronic wounds to heal. Machine learning models applied to Electronic Health Records (EHR) offer potential for early detection of non-healing wounds.

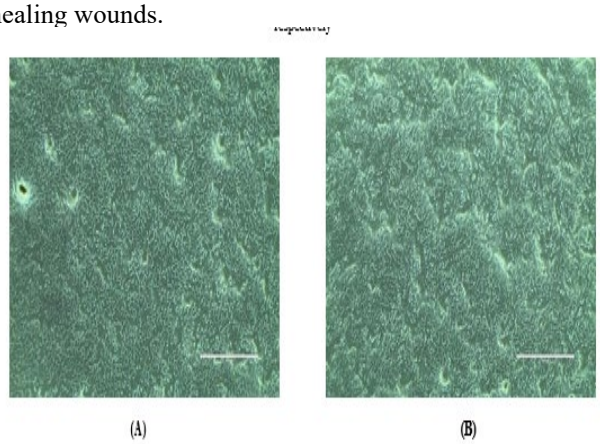

Figure 3.9 Cytotoxicity effect of (A & B) ZnNPs against 3T3 cell lines with control concentrations of 20 & 40µg/mL respectively

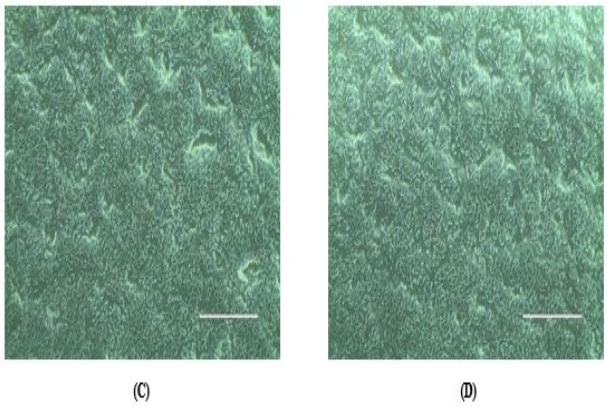

Figure 3.10 Cytotoxicity effect of (C & D) ZnNPs against 3T3 cell lines with control concentrations of 60 & 80µg/mL respectively

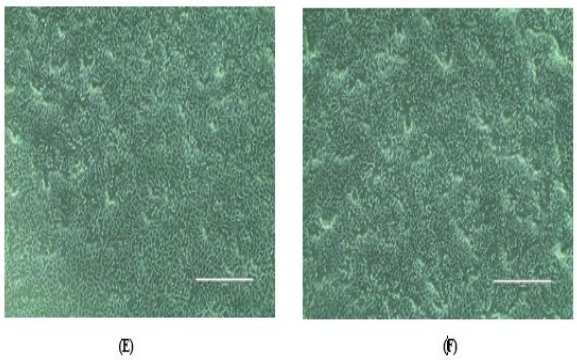

Figure 3.11 Cytotoxicity effect of (E & F) ZnNPs against 3T3 cell lines with control concentration of 100 µg/mL& control respectively

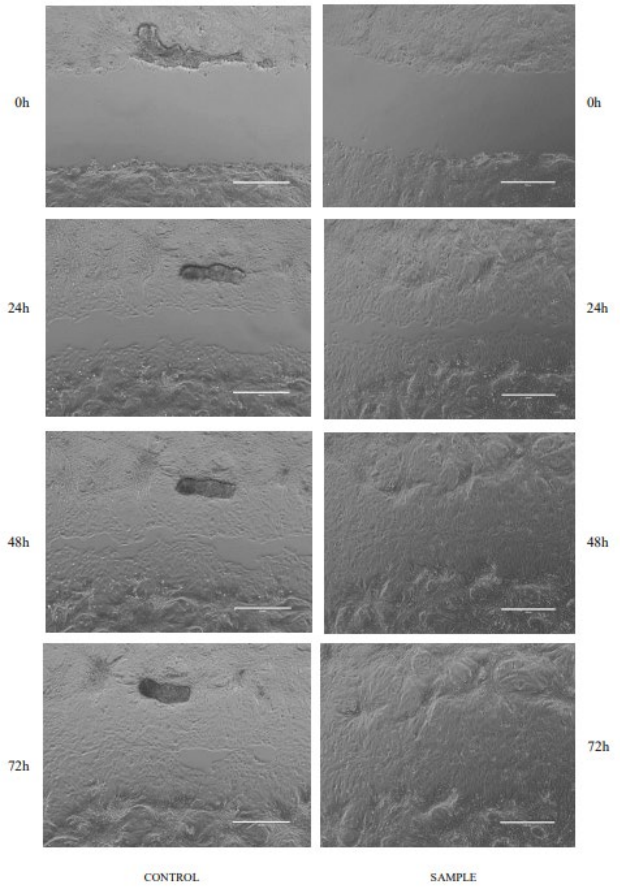

Figure 3.12 In vitro wound healing scratch assay

4. Conclusion

The research findings support the effectiveness of the PVA/Collagen/ZnNPs film in preventing microbial infections and protecting wounds and burns. The impact of ZnNPs and the film on Vero cell viability was assessed to determineany potential toxicity. It was noted that ZnNPs did not induce any notable decline in Vero cell viability, with the exception of higher concentrations. Additionally, in vitro scratch experiments conducted on the 3T3 cell line showed that the biopolymeric film containing PVA, collagen, and ZnNPs could be safely used for various biomedical applications without posing any chronic toxicity risks to cell growth and viability.

Additionally, using an inverted microscope, the efficacy of the PVA/Collagen/ZnNPs film and the pharmaceutical medicament in promoting wound healing was monitored and recorded at different time intervals of 0 hours, 24 hours, and 48 hours, and the degree of wound healing was measured. The findings show that the PVA/Collagen/ZnNPs film dramatically increased cell migration by 40.0% at 24 hours, 79.20% at 48 hours, and 97.76% at 74 hours.

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