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Evaluation of the effectiveness and chemical stability of a mixture of betamethasone, gentamicin, and zinc oxide for wound healing

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ABSTRACT

This study evaluated the efficacy of betamethasone zinc oxide (BZO), a topical compound containing zinc oxide and betamethasone G (a combination of Betamethasone 0.1% +gentamicin sulphate 0.1%, It is an antibiotic). Four formulations with varying concentrations of zinc oxide (6.25, 12.5, 18.75 and 25 gm) with 15 gm of Betamethasone G (w/w) were applied to laboratory-induced wounds in mice for 30 days to evaluate their therapeutic effects. The aim of this work was to mix compounds to find a suitable and effective formula and obtaining a compound with lower cost and study the effect of adding zinc oxide on the compound. The results showed that BG-Z significantly improved wound healing, with zinc oxide formulation (Sample 4) showing the highest therapeutic efficacy. Comparative clinical trials revealed that wounds treated with BG-Z healed faster, showed less inflammation, and had lower infection rates compared to those treated with betamethasone G alone. Physical stability testing confirmed the integrity of the formulation, with no change in color, texture, or activity at different temperatures. These results highlight betamethasone G zinc as a cost-effective and highly effective treatment for dermatological diseases, as it improves wound healing and enhances its anti-inflammatory and antimicrobial properties. This study provides a promising basis for the development of advanced topical treatments for wound management and the treatment of dermatological diseases.

Keywords: Betamethasone Zinc, Zinc oxide, Betamethasone G, Corticosteroid, Betamethasone.

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تقييم فعالية وثبات مزيج من البيتاميثازون والجنتاميسين وأكسيد الزنك في التئام الجروح

علي حسين مصطفى العبيدي

قسم الكيمياء الصيدلانية، كلية الصيدلة، جامعة تكريت، تكريت، العراق

الملخص

قيّمت هذه الدراسة فعالية بيتاميثازون أكسيد الزنك (BZO)، وهو مركب موضعي يحتوي على أكسيد الزنك وبيتاميثازون ج (مزيج من بيتاميثازون 0.1% + جنتاميسين سلفات 0.1%، وهو مضاد حيوي). طُبّقت أربع تركيبات بتركيزات متفاوتة من أكسيد الزنك (6.25، 12.5، 18.75 و25 غم) مع 15 غم من بيتاميثازون ج (وزن/وزن) على جروح مُستحثة مختبريًا لدى الفئران لمدة 30 يومًا لتقييم آثارها العلاجية. كان الهدف من هذا العمل هو خلط المركبات لإيجاد تركيبة مناسبة وفعالة، والحصول على مركب بتكلفة أقل، ودراسة تأثير إضافة أكسيد الزنك على المركب. أظهرت النتائج أن BG-Z يُحسّن بشكل ملحوظ من التئام الجروح، حيث أظهرت تركيبة أكسيد الزنك (العينة 4) أعلى فعالية علاجية. أظهرت التجارب السريرية المقارنة أن الجروح المعالجة بـ BG-Z تلتئم أسرع، وتُظهر التهابًا أقل، ومعدلات عدوى أقل مقارنةً بتلك المعالجة ببيتاميثازون جي وحده. وقد أكد اختبار الثبات الفيزيائي سلامة التركيبة، دون أي تغيير في اللون أو الملمس أو النشاط عند درجات حرارة مختلفة. تُبرز هذه النتائج بيتاميثازون جي الزنك كعلاج فعال من حيث التكلفة وعالي الفعالية للأمراض الجلدية، إذ يُحسّن التئام الجروح ويُعزز خصائصه المضادة للالتهابات والميكروبات. تُوفر هذه الدراسة أساسًا واعدًا لتطوير علاجات موضعية متقدمة لإدارة الجروح وعلاج الأمراض الجلدية.

INTRODUCTION

Betamethasone is a synthetic corticosteroid that belongs to the class of glucocorticoids, widely recognized for its strong anti-inflammatory and immunosuppressive properties. It acts by binding to intracellular glucocorticoid receptors, modulating gene transcription, and subsequently inhibiting the release of pro-inflammatory mediators such as prostaglandins and leukotrienes [(1)]. Research indicates that it is a topical anti-inflammatory treatment containing betamethasone, a potent corticosteroid. It reduces swelling, redness, and itching associated with inflammation of the skin and other tissues by suppressing the immune response and reducing capillary permeability. Previous studies have discussed the effectiveness of betamethasone valerate in treatment and in dermatology by specialists, as it has proven effective and safe in stabilizing wound healing [(2)]. Gentamicin sulfate (G), an aminoglycoside antibiotic, is widely used to combat bacterial skin infections and in the treatment of dermatological diseases. The primary mechanism of action involves interference with protein synthesis, which directly results in bacterial cell death, not merely by reducing their viability only and accelerates the healing process of infected wounds [(3)]. Numerous studies and research have examined the effect of aminoglycosides on Gram-negative bacteria. They have been incorporated into many antibiotic formulations, such as gentamicin sulfate dressings, due to their ability to effectively deliver the active ingredient, reduce the dosage frequency, and improve disease outcomes, provided patients adhere to treatment. Gentamicin treats bacterial infections and improvement in inflammatory conditions is a secondary effect of treating the underlying bacterial infection [(4)]. Laboratory studies have demonstrated the antibacterial activity of nine aminoglycosides, one of which is gentamicin sulfate [(5)]. This compound acts as an antibacterial against a wide range of harmful bacterial strains and as a topical antibiotic in the treatment of primary and secondary bacterial skin infections, highlighting its effect in inhibiting bacterial protein synthesis and preventing the spread of infection [(6)]. Zinc oxide (ZnO) is known for its broad-spectrum antibacterial, anti-inflammatory, and UV-protective properties. The European Commission has widely documented its safety and effectiveness for various uses in cosmetics and sunscreens [(7)]. The effectiveness of zinc oxide in antibacterial reactions has been confirmed by studies conducted by researchers in medical settings. ZnO nanoparticles, with the help of lasers, reduce Gram-positive bacteria (Staphylococcus aureus) [(8)]. Excessive amounts of zinc oxide nanoparticles have also been observed to have negative skin effects on some organisms whose cells resemble human cells [(9)]. Therefore, the Commission recommended caution in the use of treatments containing zinc at high and unstudied concentrations, and that the concentrations should be known and accurate. Studies have also been conducted on its use in the treatment of some types of skin cancer, where the effectiveness of these compounds against cancer cells was observed, and their activity was reduced by synthesizing polymeric compounds of chitosan with nickel (II) and zinc (II). The two prepared compounds were tested against several types of cancer cells as shown in the source [(10)]. The European Commission's Scientific Committee on Consumer Safety (SCCS) has confirmed the safety of zinc oxide as a UV filter in sunscreens [(11)]. The research concluded that zinc oxide is safe for consumers when used at concentrations up to 25% in topical applications [(12)]. Studies have also confirmed that zinc oxide's antibacterial properties, by supporting a protective skin barrier, contribute to its effectiveness in protecting and healing the skin from infections[(13)]. Mice are used in research due to their genetic and physiological similarity to humans [(14, 15)]. Mice share approximately 95% of their genes [(16-19)], making them excellent models for studying human diseases. Their short lifespan and ease of handling also facilitate research studies examining the efficacy of laboratory-prepared compounds, whether by injection, application to the affected area, or oral administration, as described in the aforementioned medical sources [(20-22)].

MATERIALS AND METHODS

Materials and Preparation of the mixture

A pharmaceutical compound consisting of zinc oxide (ZnO) 15% with mixing of Betamethasone G known as betnosam (0.1% betamethasone base and 0.1% gentamicin sulfate) both compound zinc oxide and Betamethasone G are ready formula from the State Company for Drugs and Medical Appliances Industries - Samarra (SDI), Iraq.

The mixture of Betamethasone G-Zinc for active ingredients for the treatment of skin diseases was prepared in the laboratories of the College of Pharmacy at Tikrit University. The compounds were mixed at different wight of zinc oxide (6.25, 12.5, 18.75 and 25 gm) with 15 gm of Betamethasone G (w/w), as show in Table 1. Creamy chemical compounds with different concentrations were obtained. Color and composition stability, heat and cold stability were measured for 1 year to verify the consistency and other chemical and physical properties. The compound was found to be safe for use and unchanged. The prepared sample was then placed in laboratory bottles, sealed, and transported to the Animal House Research Laboratory at the College of Veterinary Medicine, Tikrit University.

Laboratory Analysis

In this study, a new experimental pharmaceutical compound at different concentrations. was investigated. The preparations were coded as (Z-BG1, 2, 3, 4). The preparations were prepared according to international pharmaceutical dictionaries, taking into account some of the laboratory methods used in the laboratories of Samarra Pharmaceutical Company [(23)].

After coding, the samples were transferred to the animal house at the College of Veterinary Medicine, Tikrit University, to study their clinical efficacy on laboratory mice for 30 days [24]. Two swabs were applied daily, at 12-hour intervals, to the wound areas, as shown in the images.

Table 1: The mixtures of Z-BG (w/w)

Mixture Betamethasone G -zinc (Z-BG) (w/w)	Zinc oxide(Z) (w)g	Betamethasone G (BG) (w)g
Betamethasone G -zinc 1 (Z-BG1)	6.25g	15g
Betamethasone G- zinc 2 (Z-BG2)	12.5g	15g
Betamethasone G -zinc 3 (Z-BG3)	18.75g	15g
Betamethasone G - zinc 4 (Z-BG4)	25g	15g

Physical and Chemical Stability of mixture

After preparing the chemical compound required for the research, its physical properties, including its stability, were studied in the laboratory, following approved scientific protocols to ensure its purity and desired concentration. These properties included color, odor, texture, and consistency in the College of Pharmacy laboratories. The prepared compound was divided into four identical weight samples, and tests were conducted at different temperatures by placing the compound in an incubator, and visually observing changes in color, consistency, and texture throughout the year. Tests were conducted at different times of day and months of the year, using laboratory observations and measurements to verify short-term changes. Daily observations were recorded and analyzed weekly throughout the year. This helped evaluate the long-term stability of the product in a laboratory, simulating the conditions the compound might be exposed to during use or long-term storage in pharmacies or chemical warehouses. Color and consistency were observed to be stable at temperatures close to 4°C (cold temperatures), and were also stable at a laboratory temperature of 25°C. However, at higher temperatures, ranging from 40 to 60°C, oxidation occurs, and only the surface of the compound hardens. This requires that the container in which the compound is stored be tightly closed to maintain a stable viscosity. The viscosity of the samples was measured periodically (monthly or quarterly) using a viscosity meter. Based on these changes, the stability of the chemical compound under various conditions was determined. No significant changes in viscosity and color were observed, and the stability of the compound was not statistically significant. This indicates good stability.

The stability of the chemical properties was confirmed after exposing the sample to high temperature, light, and oxygen to determine whether it was oxidized. The sample was analyzed using high-performance liquid chromatography (HPLC) to determine whether the compound's metabolites had decomposed or changed their consistency, which could lead to a decrease in their activity. This was confirmed by Fourier transform infrared (FTIR) measurements at the Central Laboratory at Tikrit University. Other modern analytical techniques were also used, and the sample was sent to the Pharmaceutical Laboratories Research Center in Samarra for further testing to determine the compound's stability and composition in terms of viscosity, density, and concentration, in addition to other tests, such as nuclear magnetic resonance, as described in the research. The stability and effectiveness of the new compound were confirmed, and it could be used in pharmaceutical and therapeutic preparations in the future.

Experiment Study

A group of laboratory mice (such as house mice or Mus musculus musculus) similar in age, weight, and sex was selected for eye regeneration. Thirty-two mice, 16 males and 16 females, were selected from the animal house of the Department of Veterinary Medicine at Tikrit University and maintained in controlled environments. Clinical examination and analysis were performed on the mice after obtaining official legal and ethical approvals (No. 7/40/2157, October 29, 2023).

The groups were divided into four main groups:

Group 1: ZNO

Group 2: Betnosam

Group 3: The new in vitro-prepared cream

Group 4: Untreated

The described procedure of shaving a mouse's back and creating superficial wounds in two directions is part of a wound healing test to evaluate the effectiveness of treatments (drugs, biomaterials, or therapies) in skin regeneration, as illustrated in Figure 1. Methods used to evaluate treatment: Wound creation: Wounds are often created in two perpendicular directions (horizontally and vertically) using a scalpel to standardize wound size and depth. This allows for comparison of wound healing rates between the treated and control groups [25].

Four mixtures with different concentrations of Z-BG were applied, as shown in Table 1. The new cream (or the conventional treatment) was applied topically to the affected area of the wounds in one of the two groups, twice daily for 30 days. The blade wound areas on the skin of the mice, as shown in the image, were coated with four Z-BG preparations. The first group of male and female mice was immediately treated with Z-BG1, the second group with Z-BG2, the third group with Z-BG3, and the fourth group with Z-BG4. The remaining group was left untreated for five days to allow the infection to progress. The patients were monitored daily for any skin changes, improvement, or side effects. Data and measurements (such as wound size and swelling) were recorded periodically and regularly for each patient in each group. The most effective of the four prepared compounds was then recorded for use in the untreated group. After analyzing the results, it was observed that Z-BG4 was more effective in healing wounds, treating them in a shorter time and without leaving any side effects on the infected wound area. As shown in Figure (3), the results between the treatment group and the control group demonstrate the effectiveness of the new cream in improving the patient's condition compared to no treatment or conventional treatment, as detected and diagnosed visually. Tests were performed on mice, as described in the following sections of the study, using the same methods used in previous scientific research [26].

Fig. 1: The areas of the wound made with a blade were smeared on the skin of the mice.

RESULTS

Procedure

Wound healing efficacy was assessed using visual and metric calibrations. The wound healing rate was measured with a ruler in mm and changes in wound area were tracked over time. This wound healing rate increased with increasing zinc oxide concentration in the calibrator and the time required for healing, as shown in Figure 2 for the wounds.

3.2- Group 1 (Uninfected Wounds):

The four Z-BG mixtures demonstrated varying degrees of therapeutic efficacy in wound healing. Z-BG1 (10/15) had the weakest effect (40%), requiring prolonged treatment to achieve significant

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results. Z-BG2 (15/15) demonstrated a slight effect (50%), but still required prolonged treatment. In contrast, Z-BG3 (15/20) demonstrated moderate efficacy (65%), resulting in a shorter treatment duration. In the fourth mixture (Z-BG4, at a concentration of 25/15 g (w/w)), the best therapeutic performance (90%) was achieved, with a faster healing rate compared to the other mixtures.

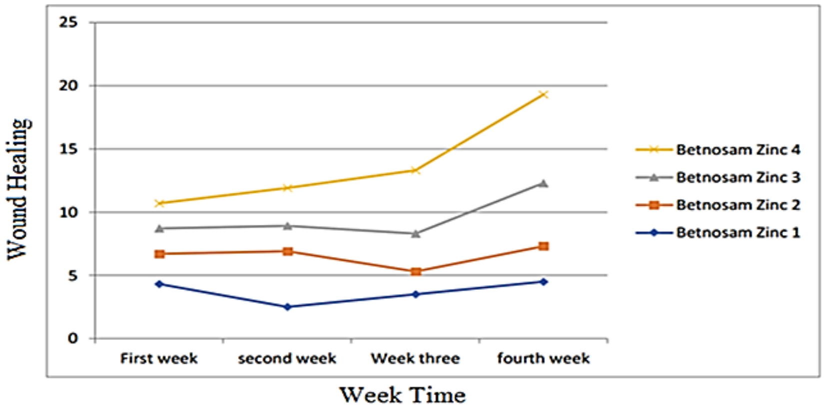

Fig. 2: Comparison of the therapeutic efficacy of the four Z-BG mixtures and healing time

Figure 2 shows the performance of four groups (Z-BG1, Z-BG2, Z-BG3, and Z-BG4) over four weeks. These groups demonstrated significantly superior wound healing compared to the other models, indicating a dose-response effect, where higher numerical values (such as zinc dose or concentration) are associated with better outcomes. The significant initial differences between the four mixtures may reflect differences in absorption rates or wound sensitivity to treatment. Based on these results, Z-BG4 appears to be the most effective option for wound treatment, while other models may require improvements in their formulation to enhance their therapeutic efficacy.

These findings suggest that the effectiveness of Z-BG in accelerating wound healing depends on its chemical composition and the skin's ability to absorb the active ingredients. The weaker effects observed in the first two models could be due to lower concentrations of active compounds or differences in their release mechanisms within the tissue. Conversely, the superior performance of the third and fourth models indicates a more balanced formulation that allows for faster absorption or a stronger impact on wound healing.

Based on these findings, Z-BG4 appears to be the most effective option for wound treatment, while the other models may require formulation improvements to enhance their therapeutic potential.

Group II-Inflamed Wounds:

Comparison of the method with previously prepared compounds and those prepared in the research labs of the College of Veterinary Medicine (Animal House) to measure the speed of wound healing in mice:

1. Mice selection: Thirty mice less than one year old and adults (15 females and 15 males) were selected for the experiments and divided into three groups:
- Group 1: treated with medicated ointment (Z, BG).
- Group 2: treated with conventional zinc oxide treatment.
- Group 3: untreated.

2. A medium-sized incision was made in the skin using a sterile scalpel in the animal barn by an animal barn specialist. The zinc-containing preparation was used to treat the wounds. The preparation was applied to the wounds of the first group of experimental mice in the animal barn, while the conventional treatment commonly used to

treat wounds was applied to the wounds of the second group, as shown in the images.

3. Evaluation of therapeutic efficacy: During the study, the efficacy of the preparation was monitored. Wound healing and its effectiveness were assessed. Healing rates and visual healing were assessed. All observations were recorded for all groups over two days, twice daily, for a full month.

CONCLUSIONS

Research results showed that the laboratory-prepared preparation, a chemical combination of gentomycin, betamethasone, and zinc oxide, produced positive results when used to treat skin infections in mice. It accelerated wound healing in the first group of mice compared to the second group, which received conventional treatment without zinc. Faster wound healing was observed in the zinc-containing preparation compared to the second group of mice that did not receive zinc. These results suggest that this compound may help accelerate skin tissue regeneration and reduce inflammation, making it a more effective treatment option compared to other treatments, as shown in Figure 4. This treatment could be a new, effective, and promising treatment for skin infections in the future.

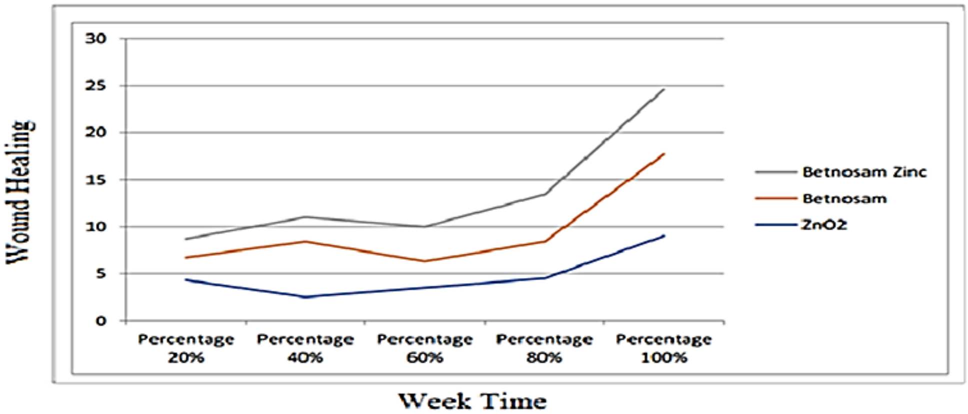

Fig. 3: shows a comparison between (Z, BG and Z-BG)

1. Effect of Gentomycin:

Mechanism of Action: It kills bacteria by inhibiting their growth and preventing protein synthesis in the bacterial cell. Gentomycin has a broad spectrum of activity against various types of Gram-negative bacteria and some strains of Staphylococcus [27].

2. Effect of Betamethasone:

Mechanism of Action: Betamethasone is used to treat inflammation. Corticosteroids, such as betamethasone, are generally considered anti-inflammatory agents in hospitals. They work by suppressing the body's immune response, reducing symptoms of inflammation such as redness, swelling, and itching [28].

3. Evaluation of the Effect of Zinc Oxide:

Mechanism of Action: Zinc oxide acts as a skin protectant, forming a protective layer on the skin's surface that protects it from moisture and irritants, helping to keep it dry and speeding up the healing process. It is also used in many medical products [29]. Reducing bacterial infections, reducing symptoms of inflammation, protecting the skin, and accelerating its healing [30]. The final results depend on several factors, including the type and severity of the infection, the dosage of the medication used, and the duration of treatment. It is recommended to conduct specialized scientific studies to accurately evaluate the effectiveness of this formula [31].

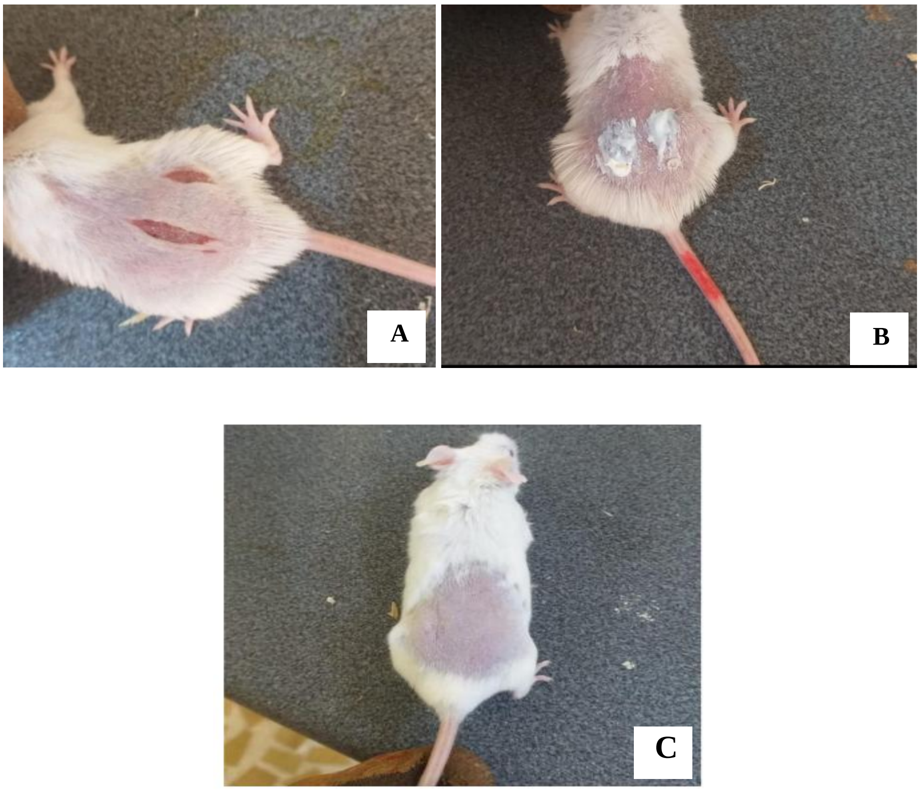

Fig. 4: The mice a) before, b) with treatment and c) after treatment complete healing of wounds after using the Z-BG

Physical and Chemical Stability

One-year exposure of mixtures under a variety of temperature and light did not alter physical properties. Color of mixture it was the same and viscosity it was 25000 Cp at 25 C°. Density were 1.05 g/cm^3 at 25 C°.

Laboratory Analysis: Chemical analysis of the four formulation was done in Samarra Drug Industry laboratories; the IR spectrum based on the functional groups in the Figure 4, to identify the main functional groups present, figure 5 show the NMR spectrum of the Z-BG structure in the image, the following functional groups are observed: Possible Zn coordination effect, which may slightly shift these peaks.

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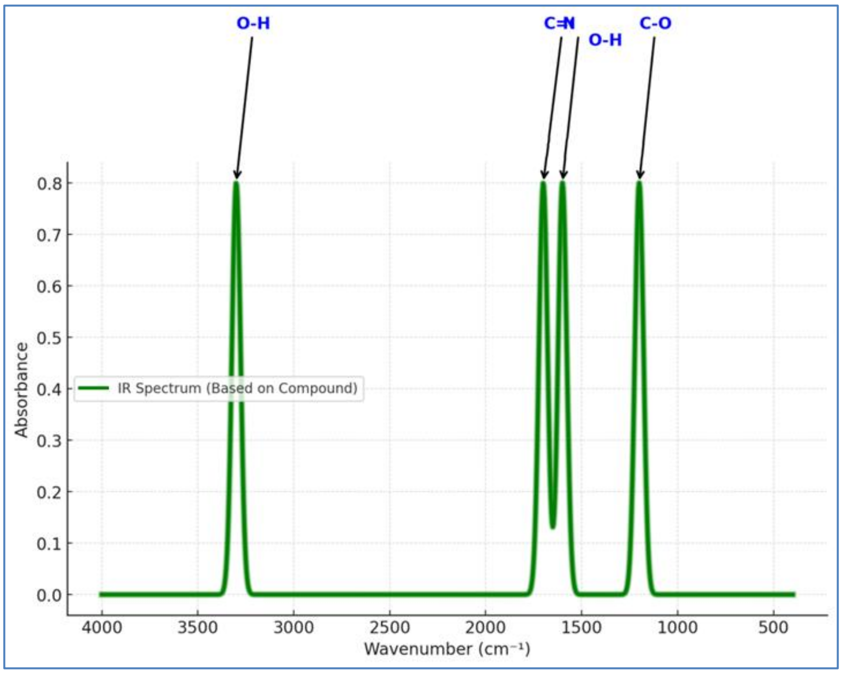

Fig. 5: IR Spectrum of Z-BG

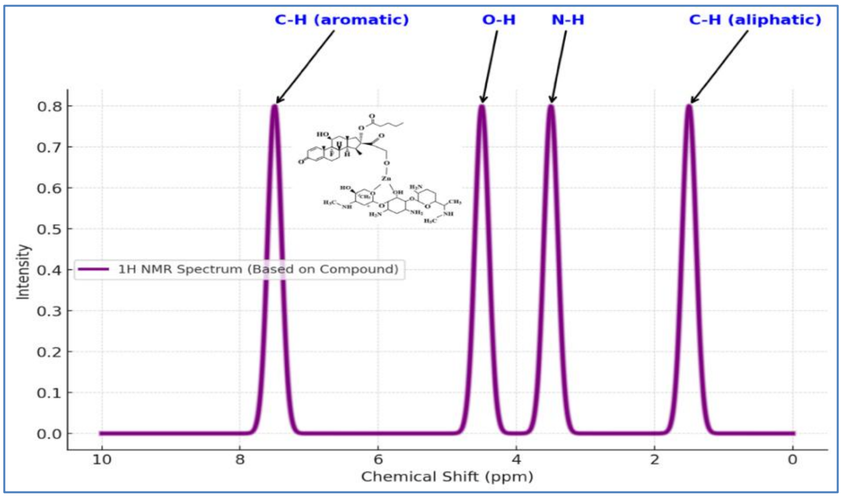

Fig. 6: NMR Spectrum of Z-BG

DISCUSSION

Chronic inflammation is widely recognized as a major barrier to wound healing, primarily due to its role in prolonging the inflammatory phase, elevating levels of oxidative stress, and impairing key regenerative processes such as fibroblast and extracellular matrix synthesis [32]. Zinc plays a critical role in modulating immune responses, promoting re-epithelialization, and enhancing collagen synthesis, facilitating faster wound repair [33]. These findings underscore the clinical importance of controlling inflammation in wound management. Evidence suggests that interventions targeting inflammation, whether through pharmacological agents or micronutrient supplements such as zinc, can significantly improve healing outcomes, particularly in cases of chronic or complex wounds [34]. Thus, the observed disparity in healing rates between the two groups reinforces the therapeutic potential of zinc-based therapies and supports the need for further research into their formulation and optimal application in infected wounds.

CONCLUSIONS

This study demonstrated that Z-BG4 (15/25) (w/w), particularly the 15-gram zinc oxide formulation, significantly enhanced wound healing in both infected and non-infected wounds, providing a stable and cost-effective treatment. The synergistic effect of zinc oxide with betamethasone and gentamicin sulfate demonstrated superiority over the individual components in terms of efficacy and pharmacological stability.

Group 1 (non-infected wounds): This group demonstrated rapid and effective healing, with a gradual decrease in wound size until complete healing (100%) by week 4.

Group 2 (infected wounds): This group demonstrated delayed wound healing, with the wound not fully healing and only reaching approximately 60% to 80% healing by the end of the study period.

Interpretation

These results are consistent with previous studies indicating that chronic inflammation impedes wound healing. This is due to several factors, including:

Long inflammatory phase.

Increased oxidative stress.

Impaired basic regenerative processes (such as fibroblast activity and extracellular matrix formation).

This study recommends further validation of the results through advanced chemical analyses and clinical trials on human skin to investigate side effects and optimize the formulation. Successful results may lead to the inclusion of Z-BG as a new standard treatment for wounds and skin allergies.

Conflict of Interest

The researchers declare that they have no conflict of interest.

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