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Development of Beta-Carotene Extract and Caffeine Hydrogel-Based for Wound Healing

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Abstract

The skin, as the largest organ in the human body, plays a vital role in protecting the body from external damage and microbial invasion, while maintaining the balance of fluids, electrolytes, and essential nutrients. Skin injuries, often resulting from accidents, can lead to wounds that require prompt healing to prevent complications and infections. The use of preparation containing natural antioxidant agents is an essential part of wound care. Recent studies continue to explore various materials for wound healing, with hydrogels emerging as an effective delivery system due to their unique properties. This study aims to formulate a beta-carotene hydrogel and caffeine polymer-based topical gel for wound healing and protection. The objectives of this research are to evaluate the physical properties, pH, viscosity, and spreadability of the hydrogel over a storage period of 28 and 56 days. Additionally, the study investigates wound healing effectiveness in animal models 28 rats are divided into three groups, each containing 4 rats. by assessing the healing time, collagen formation, Ephitalization, and fibroblast over a 3-week period. The results analyzed using ANOVA, with a significance level of $p < 0.05$. Previous research has demonstrated that beta-carotene, isolated from carrot extracts, and nano-caffeine formulations have shown promising results in wound healing. The findings of this study are expected to contribute valuable insights into the development of effective topical treatments. This research offers a potential advancement in the field of wound care and topical drug delivery systems.

***Keywords**: Beta Carotene, Caffeine, Wound Healing, Hydrogel-Based, Ephitalization*

Introduction

Skin is the largest organ in the human body and plays a critical role in protecting the body from external threats, such as microbial infections and physical damage. Skin injuries, resulting from accidents or other trauma, require proper management to prevent infection and facilitate wound healing. One effective method to support wound healing is the use of drug delivery systems based on hydrogels. Hydrogels are advantageous because they can retain moisture, which is crucial for wound healing, and they provide a platform for the gradual delivery of active substances to the wound site.[1] Wounds, particularly burn injuries and chronic wounds, are common medical issues that significantly impact the quality of life of patients. Effective wound healing is crucial for reducing complications and promoting the recovery of tissue. Various therapeutic approaches have been developed to accelerate wound healing, one of which is the use of nanoparticles and hydrogels based on biomaterials.[2]

Chitosan, a polysaccharide derived from the exoskeletons of crustaceans, has demonstrated antioxidant and antimicrobial properties that can aid in wound healing. When incorporated into hydrogel formulations, chitosan enhances wound healing by reducing inflammation and promoting tissue regeneration.[3] Additionally, beta-carotene, a provitamin A, is recognized for its antioxidant properties that can reduce oxidative stress in wounds and support cellular regeneration.[4] Caffeine, on the other hand, has been shown to positively influence wound healing by improving microcirculation and stimulating collagen formation.[5]

Nanoparticles are nanoscale particles that can encapsulate various active compounds, including pharmacological agents, to enhance therapeutic efficacy and prolong drug release.[6] Caffeine, a compound known for its anti-inflammatory properties and its role in enhancing wound healing, has shown potential in

wound therapy. The synthesis of caffeine nanoparticles from Pagar Alam tea extract, which is rich in antioxidants, holds promise for providing synergistic effects in enhancing the healing process.[7] On the other hand, hydrogels are delivery systems commonly used in wound care due to their ability to maintain moisture and create an environment conducive to tissue regeneration.[1] Beta-carotene, a potent antioxidant, has been widely studied for its ability to accelerate wound healing. Beta-carotene-based hydrogels can offer additional benefits through the controlled release of this compound to the wound site.[8] Recent research has focused on combining these ingredients to enhance the effectiveness of hydrogels in wound healing.[9] Therefore, this study aims to develop and evaluate hydrogel formulations containing beta-carotene and caffeine as active ingredients for wound healing, with chitosan used as the carrier material. Physical testing and wound healing evaluations using animal models are expected to provide further evidence on the potential of this hydrogel drug delivery system.

Methods

Materials

Carbopol (Colorcon, USA), Gelatin, Glycerin (Brataco), Propylene Glycol (Brataco), Methyl Paraben (Brataco), Propyl Paraben (Brataco), Chitosan (Medi), PVP, Agarose (Merck), NaCl 0.9% infusion (Otsuka), Glycerin, TEA, Chitosan, Na Alginate, Bioplacenton®, H&E stain, Paraffin, Formalin 10%, Ethanol, Xylene, Ketamin HCl (Bernofarm).

Equipment

Thermometers, scissors, cotton, tweezers, bandages, microscope, caliper, pH meter, Brookfield Rotary viscometer, Horiba Sonicator.

Animal Model

Male Wistar strain white rats (Rattus norvegicus), aged 3 months with a body weight of approximately 150-200 g.

Formulation of Hydrogel

The process of making the hydrogel begins with the development of each hydrogel base in 20 mL of distillate water (DW) for 2 hours. Mixture one is made by slowly adding carbopol, gelatin, and CMC into a beaker while stirring with a mixer (Mixture 1). Once homogeneous, glycerin and propylene glycol are added slowly until homogeneous. Then, TEA is added slowly while stirring, and the pH of the mixture is measured as Mixture 2.

Distillate water is added slowly while stirring, and the mixture is weighed until the weight reaches approximately 100 g. The beaker is covered with aluminum foil and sterilized in an autoclave at 121°C for 15 minutes. Mixture 3 is made by dissolving 5 g of chitosan 0.5% in 10 mL of ethanol. Ultrasound is applied for 1 minute and then mixed with Mixture 2 gradually until homogeneous to obtain Mixture 5. Mixture 4 is made by dissolving 2 g of caffeine in 5 mL of hot water and 5 mL of ethanol. Mixture 4 is added to Mixture 5 gradually while stirring until homogeneous, forming Mixture 6. Hydrogel is prepared using the active ingredient from Mixture 6 and subjected to ultrasound for 3 to 5 minutes. Stir until homogeneous.

Hydrogel Characterization Testing

a. *Physical Observation*: Physical observations of the hydrogel are made subjectively, such as color and appearance. B. pH Measurement: pH of the hydrogel is measured using a digital pH meter (Oakton-Eutech instruments). The glass electrode of the pH meter is dipped into the hydrogel, and the pH value is displayed on the indicator screen.
b. *Viscosity Measurement*: Viscosity is measured using a viscometer (Rion viscotester VT-04F). 200 g of hydrogel is placed in a special beaker, and spindle no. 2 is immersed into the hydrogel. The viscometer is turned on, and the viscosity reading is taken when the needle stabilizes.
c. *Spreadability Measurement*: Two glass plates are used, one with a millimeter block for ease of observation and measurement, while the other is used as a cover. 1 g of hydrogel is placed in the center of the glass plate. The hydrogel is covered with the other plate and weighted with a total weight of 125 g for 1 minute. The spreadability is measured by calculating the area of the formed zone (cm^2) using the formula πr^2.

Burn Wound Preparation in Rats

The rats are adapted for one week and provided with measured food and unlimited water. Anesthesia is performed with Ketamin HCL (Bernofarm) until the rats no longer feel sensation, but their breathing remains normal. The fur on the back of each rat is shaved. The burn wound is created using a hot aluminum plate (80°C) with a 2.5 cm diameter, placed on the skin for 20 seconds.

Treatment Grouping

Twenty-eight (28) rats are divided into three groups, each containing 4 rats. The first group is treated with 0.9% NaCl solution as a negative control. The second group is treated with Bioplacenton® as a positive control. The third group is treated with the hydrogel formulation. The gel is applied to the burn wound at 350 mg twice a day. After each application, the wound is covered with bandages to prevent contamination. The rats are housed in separate cages and provided with the same amount and type of food and water.

Assessment of Burn Wound Healing and Tissue Collection

Skin tissue is collected from the rats on the 3rd day (inflammatory phase) and the 7th day (proliferative phase). Three rats from each phase are sacrificed by Anesthesia. Specimens from the burn wounds are excised with a diameter of about 2 cm down to the muscle layer. The collected skin tissue is placed in formalin 10% for fixation. Macrophage and fibroblast counts are performed with Hematoxylin-Eosin staining. The number of macrophages and fibroblasts is observed under a microscope at 40x magnification by counting active cells in each field of view from the top-left to bottom-right corners. Macrophages appear irregularly shaped with bluish color and brown granules in the cytoplasm, while fibroblasts appear in clusters with red cytoplasm. Collagen is observed by visual.

Burn Wound Healing Assessment

Burn wound healing is assessed daily by observing the color, dryness, and diameter of the wound using a caliper. Each change in the wound area is recorded and calculated to determine the healing process. The percentage of burn wound healing is calculated using Equation 1.

$$p_x = 100 - \left(\frac{dx}{d}\right) x100$$

Equation 1. The percentage of burn wound healing
Note: where px is percentage of wound healing on day x; d is burn wound diameter on the first day; d_x is burn wound diameter on day x

Preparation of Caffeine Nanoparticles Using 0.25% Chitosan

Caffeine nanoparticles are prepared using the method of Marlidyanti et al., 2011. Caffeine (1 gram) is dissolved in 50 mL of 0.25% chitosan in 3% acetic acid and homogenized using a stirrer at 200 rpm. The suspension is then resuspended in 10 mL of WD until a stable suspension is formed. Centrifugation at >5000 rpm is performed to obtain a stable nanosuspension.

Preparation of PVA

Amount 2.5 g of PVA powder is dissolved in 100 mL of WD at 60°C and stirred for 24 hours at 75 rpm until homogeneous. The PVA solution is measured to ensure the appropriate concentration for each formula.

Table 1. Hydrogel Formulation

No	Ingredient	F1	F2	F3
1	Beta-carotene	2.5%	2.5%	2.5%
2	Caffeine	2%	2%	2%
3	Carbopol	0.834	0.834	0.834
4	CMC	0.147	0.147	0.147
5	Gelatin	0.6	0.6	0.6
6	Glycerin	12.5	12.5	12.5
7	PEG	2	2	2
8	TEA	3	3	3
9	Chitosan	-	0.2	0.5
10	Methyl Paraben	0.02	0.02	0.02
11	Propyl Paraben	0.18	0.18	0.18
12	PVP	0.5	0.5	
13	Water distillation up to	100 g	100 g	100 g

Result

Skin Irritation Test

To test the irritation formulation, skin irritation trials were performed on male Wistar rats. The fur on the back of the animals was shaved using a hair clipper one day before the testing procedure. The animals were then randomly divided into four groups, each consisting of three rats. In the first group, a nanohydrogel containing Beta-Carotene Gel was applied to the shaved area. The second and third groups were given a hydrogel containing Beta-Carotene Gel, while the fourth group received a gel containing Beta-Carotene Gel. Rats that were given saline solution and no drug formulation served as the control group.

The formulations being tested were applied evenly to the shaved area and covered with gauze. Any sensitivity reactions, such as edema or erythema (redness), were observed at 1 hour, 8 hours, and 24 hours after the treatment. The Draize scale was used to evaluate skin irritation. The irritation score ranged from 0 (no response) to 4 (severe response) to assess intensity.

Table 2. Skin Irritation Test Score

Group	Edema	Redness (Erythema)	Other Forms	Total Score
I Control (3)	1	1	1	4
II BC (3)	1	1	1	4
III Bioplacenton (3)	1	1	1	4
IV (Base) (3)	1	1	1	4

Note: The scoring system ranges from 1 to 5. A score of 4 indicates no significant difference in skin irritation, edema, erythema, or other forms between the test groups.

The study of skin irritation highlights one of the major challenges in topical therapy. The research results indicate that gels containing Beta-Carotene, hydrogels containing Beta-Carotene, and nanohydrogels containing Beta-Carotene did not cause any skin irritation, even after 24 hours of applying these formulations. No signs of erythema or edema were observed in any of the animals. This finding suggests that other formulations containing Beta-Carotene can be well-tolerated and do not induce skin sensitivity. Therefore, nanohydrogels containing Beta-Carotene could be considered a safe and well-tolerated delivery method for topical application.

a. Infrared (IR) Examination of Beta-Carotene

The Infrared (IR) spectrum of Beta-Carotene was analyzed to determine its characteristic functional groups and bonding types. The key functional groups observed in the IR spectrum of Beta-Carotene include the C-H stretch, C=C stretch, and C-H bending vibrations, which are typical of the conjugated polyene structure of Beta-Carotene. Specific peaks at: 2950 cm^{-1} corresponding to C-H stretching vibrations,1640 cm^{-1} indicative of the conjugated C=C stretching, 1450 cm^{-1} representing C-H bending vibrations. These peaks confirm the chemical structure of Beta-Carotene and its conjugated system of double bonds, which is responsible for its biological activity and color.

b. UV-Vis Examination of Beta-Carotene

The UV-Vis spectrum of Beta-Carotene was also recorded to examine its absorbance characteristics. The Beta-Carotene showed strong absorption in the UV region, particularly around 450 nm, which corresponds to the characteristic absorption peak for Beta-Carotene due to the conjugated polyene chain. The absorption spectrum indicates the presence of extended conjugation within the Beta-Carotene molecule, which contributes to its antioxidant properties and photochemical stability. The observed absorbance is consistent with the known properties of Beta-Carotene in both UV and visible light regions, confirming the presence of the compound and its potential for use in pharmaceutical and cosmetic formulations.

Wound Diameter of Rat Skin Tissue

The wound diameter of rat skin tissue was measured on Days 1, 5, 10, 14, 20, and 24 following treatments with Beta-Carotene gel, Bioplasenton, Base Gel, and the negative control. The results are presented as mean ± standard deviation (SD**)** for each treatment group (n = 4), as shown in Table 3.

The illustrates the changes in wound diameter in rats treated with Beta-Carotene gel, Bioplasenton, Base Gel, and the negative control over a 24-day observation period showed in Figure 1. A progressive reduction in wound diameter was observed in all treatment groups from Day 1 (D1) to Day 24 (D24), indicating continuous wound healing. The Bioplasenton group exhibited the most rapid reduction in wound diameter throughout the study, resulting in the smallest mean wound diameter at the end of the observation period. The Beta-Carotene group also demonstrated a marked and consistent decrease in wound diameter, with a greater rate of wound contraction than the Base Gel and negative control groups. In contrast, the Base Gel group showed a slower reduction in wound diameter, whereas the negative control group consistently

exhibited the largest wound diameter across the observation period, indicating delayed wound healing. Overall, these findings suggest that Beta-Carotene gel enhances wound healing by promoting wound contraction, although its effectiveness remained lower than that of the positive control (Bioplasenton).

Table 3. Changes in Wound Diameter (cm) Following Treatment with Beta-Carotene Gel, Bioplasenton, Base Gel, and Negative Control in Rats During the Experimental Period (Mean ± SD, n = 4).

Treatment Group	D1 (Mean ± SD)	D5 (Mean ± SD)	D10 (Mean ± SD)	D14 (Mean ± SD)	D20 (Mean ± SD)	D24 (Mean ± SD)
Beta-Carotene	2.505 ± 0.042	2.075 ± 0.096	0.928 ± 0.032	0.828 ± 0.032	0.638 ± 0.035	0.500 ± 0.016
Bioplasenton	2.228 ± 0.032	1.810 ± 0.014	0.718 ± 0.024	0.533 ± 0.039	0.338 ± 0.048	0.278 ± 0.021
K− (Control)	2.715 ± 0.019	2.325 ± 0.065	2.100 ± 0.082	1.915 ± 0.024	1.299 ± 0.059	0.738 ± 0.048
Base Gel	2.618 ± 0.024	2.238 ± 0.048	2.075 ± 0.096	1.893 ± 0.010	1.287 ± 0.278	0.688 ± 0.085

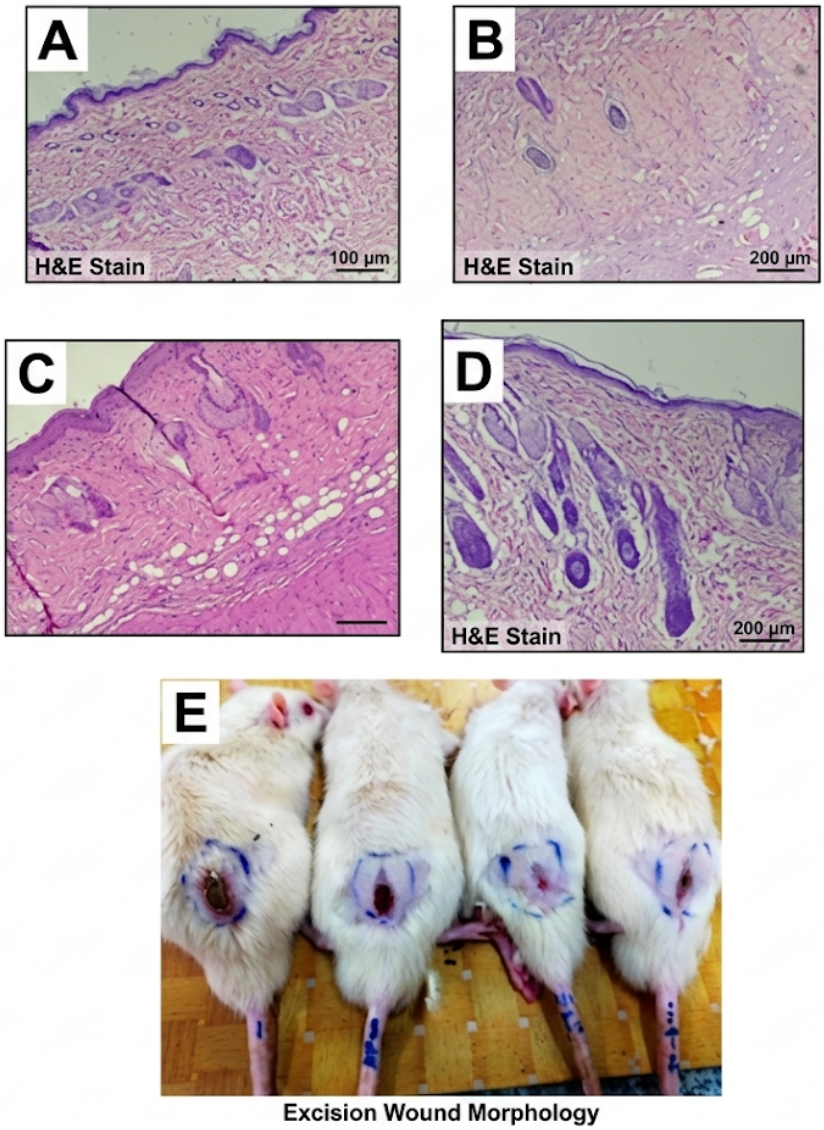

Figure 1. Macroscopic and microscopic evaluation of tissue repair during wound healing. (A–D) Histological sections of skin tissues stained with hematoxylin and eosin (H&E) from different experimental groups: (A) Negative control], (B) Positive control, (C) Beta-Carotene, and (D) Beta-Carotene formula dose 2, (E) Morphological and macroscopic appearance of excision wounds in rats on day 24.

Discussion

Macroscopic Evaluation of Wound Diameter and Healing Kinetics

Analysis of the wound diameter across all treatment groups demonstrated a progressive reduction from Day 1 (D1) to Day 24 (D24). This continuous decline indicates the successfully ongoing physiological process of wound healing, with varying degrees of efficacy observed among the groups. The kinetic contraction of the wound diameter can be divided into three distinct chronological phases, corresponding to the biological stages of tissue repair: Early Phase (D1–D10): All groups exhibited a high decrease in wound diameter. This rapid contraction is highly indicative of the early phases of healing, dominated by hemostasis, inflammation, and the initiation of granulation tissue formation.[10] Proliferative Phase (D10–D20): The rate of diameter reduction began to decelerate. During this period, the healing mechanism shifts toward cellular proliferation, angiogenesis, and initial extracellular matrix (ECM) deposition.[11] Maturation and Remodeling Phase (D20–D24): The reduction in wound size became more gradual, reflecting the final phase of tissue repair where collagen remodeling and scar maturation take place.[12] At the final observation endpoint (D24), the therapeutic efficacy based on the smallest average wound diameter was ranked as follows: Bioplasenton > Beta-Carotene > Base Gel > Negative Control (K-).

Bioplasenton Group: Demonstrated the most prominent acceleration in wound healing, with the diameter dropping sharply from 2.2275 mm (D1) to 0.2775 mm (D24). This superior outcome is attributed to the placenta extract and neomycin in Bioplasenton, which are known to strongly stimulate cell metabolism, promote fibroblast proliferation, and prevent secondary bacterial infections that stall healing pathways.[13]

Beta-Carotene Group: Exhibited highly effective wound healing activity, reducing the wound diameter from 2.505 mm (D1) to 0.5 mm (D24). This significant acceleration is mediated by its robust antioxidant properties, which mitigate oxidative stress at the injury site, scavenge reactive oxygen species (ROS), and stimulate rapid tissue regeneration.[14] Base Gel Group: Showed a diameter reduction from 2.6175 mm (D1) to 0.6375 mm (D24). While it provided basic mechanical protection and moisture retention for the wound bed, it lacked the significant therapeutic acceleration observed in the active groups.[15]

Negative Control Group (K-): Displayed the slowest healing kinetic, moving from 2.715 mm (D1) to 0.9625 mm (D24). Without any intervention, the wound healed purely through natural physiological mechanisms, which proved to be the least efficient.

Microscopic and Molecular Mechanisms of Tissue Regeneration

The macroscopic findings are strongly supported by microscopic and histopathological observations. Wound area measurements on critical checkpoint days (Days 4, 11, and 18) confirmed that the Beta-Carotene gel formulation promoted the highest percentage of wound contraction by Day 18. This accelerated closing of acute wounds is further corroborated by the enhanced epithelial thickness observed under the microscope.

Re-epithelialization is a fundamental cornerstone of successful wound closure. In this study, epithelial regeneration initiated around Day 3 post-injury and maintained consistent growth up to Day 15. The thickness of this newly formed epithelial layer directly reflects the therapeutic performance of the applied formulas.[16] The multi-targeted efficacy of the Beta-Carotene gel can be linked to its intrinsic antioxidant, antibacterial, and pro-angiogenic activities.

At the molecular level, both Beta-Carotene (BC) and Bioplasenton (BP) appear to upregulate the expression of Vascular Endothelial Growth Factor (VEGF). VEGF is a critical signaling molecule secreted by endothelial cells and macrophages that induces vascular permeability, endothelial cell differentiation, proliferation, and migration, thereby driving robust angiogenesis.[17] Concurrently, the upregulation of VEGF stimulates fibroblasts to increase the production of hydroxyproline, an amino acid that serves as a direct biochemical marker for collagen content.[18] Fibroblasts play a pivotal role in synthesizing the extracellular matrix during granulation tissue formation.

As the proliferative phase transitions into the maturation phase, these hydroxyproline levels naturally begin to decline. During this remodeling stage, temporary Type III collagen is enzymatically degraded and replaced by organized Type I collagen.[19] This structural shift is essential for restoring the tensile strength of the skin, as Type I collagen forms significantly larger, thicker, and more cross-linked fibrils compared to Type III.

Therapeutic Implications on Burn Wound Management

The skin serves as the body's largest organ and a highly complex barrier responsible for protection against mechanical stress, microbial invasion, fluid loss, and thermal dysregulation. Maintaining skin integrity is therefore vital for physiological homeostasis. In this study, second-degree burn wounds—induced by controlled exposure to hot metal at 75°C for 10 seconds—showed profound structural recovery over the 24-day observation period when treated with active formulations.[20]

By Day 24, the Beta-Carotene treatment group displayed optimal effect and structural outcomes. Literature suggests that while overly elevated systemic Beta-Carotene levels can sometimes be found in abnormal hypertrophic scars, the balanced topical application of the Beta-Carotene gel formulation in this study supports normal tissue remodeling without triggering hypertrophic scar formation.[21] Overall, these findings showed the clinical relevance of active topical interventions, particularly Beta-Carotene and Bioplasenton, in accelerating cell proliferation, enhancing neovascularization, and optimizing collagen remodeling in burn wound therapy.

Conclusions

In this study, hydrogel beta carotene exhibited are expected to contribute valuable insights into the development of effective topical treatments, in the full-thickness skin injury of Wistar burn injury. This research offers a potential advancement in the field of wound care and topical drug delivery.

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