JTL 14 (1) JUNE 2025
Page: 12-20
Contents list available at Jurnal Teknologi Laboratorium

JURNAL TEKNOLOGI LABORATORIUM

Journal Homepage: www.teknolabjournal.com
ISSN 2580-0191(Online) I ISSN 2338 – 5634(Print)

Original Research

OPEN ACCESS

Cork fish extract hydrogel: A promising therapeutic agent for subcutaneous wound healing in male wistar rats

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Abstract: This study evaluated the effectiveness of a 15% cork fish extract hydrogel in promoting subcutaneous wound healing in male Wistar rats. The objectives were to examine its impact on wound healing, eosinophil counts, allergic reactions, and body weight changes. A total of 30 male Wistar rats aged 6–8 weeks (150–200 g) were randomly assigned to six groups: 15%, 10%, and 5% cork fish hydrogel treatments, positive control (Bioplacenton), negative control, and normal control. Statistical analysis using the Kruskal-Wallis test revealed significant effects of hydrogel treatments on eosinophil counts ($p = 0.032$), while ANOVA showed significant differences in wound diameter reduction ($p = 0.011$). Spearman correlation analysis identified a moderate positive correlation between eosinophil count and wound shrinkage ($r = 0.420$, $p = 0.037$). No adverse effects or allergic reactions were observed in any treatment group, and body weight remained unaffected ($p = 0.365$). These findings indicate that the 15% cork fish hydrogel effectively enhances wound healing in rats, demonstrating its potential as a safe and effective therapeutic agent for subcutaneous wound management.

Keywords: Cork fish extract hydrogel; Subcutaneous wound healing; Male Wistar rats; Eosinophil counts; Wound diameter reduction

INTRODUCTION

The medical industry, including the field of medicinal herbs, has recently seen significant innovations in wound care development.[1–6] Despite these advancements, existing clinical wound dressings still face limitations, including poor elasticity and the potential to cause irritation when replaced.[7–8] Hydrogels have emerged as a promising solution due to their elastic and non-irritative properties.[9] With their sheet-like structure and high water content, hydrogels resemble natural tissues, offering excellent water retention to keep wounds moist while absorbing exudates.[10–11] Additionally, hydrogels are stable in acidic environments, making them ideal for wound treatment.[12] These characteristics have positioned hydrogels as an alternative wound dressing for low to profuse exudate wounds, burns, ulcers, and for facilitating autolysis, scab removal, and wound cleansing.[10,13–14]

Subcutaneous wounds, which occur below the reticular dermis layer, are categorized as full-thickness wounds.[15–18] They vary in depth, ranging from superficial wounds limited to the epidermis to partial-thickness wounds involving the dermis and full-thickness wounds encompassing all layers, including subcutaneous tissue, fascia, and muscle.[15–17] These wounds follow a structured

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DOI: 10.29238/teknolabjournal.v14i1.511
Received 14 July 2024; Received in revised form 14 January 2025; Accepted 20 January 2025
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healing process consisting of hemostasis, inflammation, migration, proliferation, and maturation stages.[19] Effective wound care emphasizes maintaining a closed and moist environment to prevent fluid loss and enhance recovery. Moist conditions accelerate fibrinolysis, angiogenesis, growth factor formation, active cell formation, and reduce infection risks.[20–21]

Hydrogels, as gel-form alternatives to hydrocolloids, excel in creating a moist wound environment while absorbing exudates.[22–23] Several commercial products, including Cutimed Gel, Intrasite Gel, and Duoderm Gel, demonstrate the clinical efficacy of hydrogels.[23–25] Despite their broad application, opportunities remain for innovative natural-based hydrogel formulations with enhanced therapeutic potential.

In this research, a novel hydrogel derived from cork fish extract (*Channa striata*) was developed and applied to subcutaneous wounds. The study evaluates the hydrogel's effectiveness in promoting wound healing by observing eosinophil counts, body weight changes, and wound diameter reduction. To the best of our knowledge, no previous studies have reported on the use of cork fish extract-based hydrogels for subcutaneous wound care. This research fills a critical gap by exploring a natural-based wound dressing with the potential to offer safe, effective, and sustainable therapeutic options for subcutaneous wound management.

MATERIALS AND METHOD

Materials

The materials used in this study included cork fish extract (*Channa striata*), male Wistar rats (*Rattus norvegicus*), rat pellets, tap water, tissue, filter paper, 10% ketamine (Merck), cotton wool, 2.5% Carboxymethyl cellulose (CMC; Merck), 0.2% Nipagin (Merck), 0.1% Nipasol (Merck), 15% propylene glycol (Merck), 5% glycerin (Merck), and distilled water (ad 100%).

Hydrogel Fabrication

Hydrogel preparation began with the dissolution of Carboxymethyl cellulose (CMC) in distilled water, left to stand for 24 hours. Cork fish extract was dissolved in 70% ethanol under continuous stirring until fully dissolved. Nipagin was dissolved in hot water, followed by the gradual addition of glycerin with constant stirring. Propylene glycol was dissolved in Nipasol in a separate container. All components were thoroughly mixed until a homogeneous mixture was achieved. The resulting mixture was homogenized at 400 rpm and left to stand for 24 hours to dissipate air bubbles. The hydrogel was then dried in an oven at 40°C for 4 hours and cut into 2×2 cm pieces.[9]

Experimental Animals and Grouping

Thirty male Wistar rats (*Rattus norvegicus*), aged 6–8 weeks and weighing 150–200 g, were acclimatized for one week before the experiment. The rats were randomly divided into six groups, each comprising five rats.[26] The groups were treated as follows:

- **Group 1:** Cork fish hydrogel (15%)
- **Group 2:** Cork fish hydrogel (10%)
- **Group 3:** Cork fish hydrogel (5%)
- **Group 4 (Positive Control):** Hydrogel containing bioplacenton
- **Group 5 (Negative Control):** No special treatment
- **Group 6 (Normal Control):** No wounds or cuts

During the experiment, all groups were provided with regular food and water.[27–29]

Observation of Allergic Reactions

Allergic reactions were observed at 24 and 72 hours post-treatment using a scoring system to evaluate erythema and edema.

Erythema scoring: 0 = no erythema, 1 = very slight, 2 = clearly demarcated, 3 = moderate to severe, 4 = severe and crusted.

Edema scoring: 0 = no edema, 1 = very slight, 2 = clearly demarcated, 3 = moderate (edges rise ~1 mm), 4 = severe (edges rise >1 mm and widespread).

The Primary Irritation Index was classified as follows: <2 = not visible, 2–5 = moderate, >6 = severe.[30,31]

Assessment of Adverse Effects and Wound Healing

Adverse effects of the cork fish hydrogel were evaluated on days 1, 7, and 15, focusing on symptoms such as skin changes, fur quality, convulsions, tremors, coma, and mortality. Wound diameter measurements were performed on days 0, 3, 9, and 15. On day 15, clinical assessments included observations of eye and oral mucosa changes, rash, and inflammation. Body weight was measured before treatment, at 15 days post-treatment, and for surviving animals before used.[32,33]

Statistical Analysis

Data were analyzed using SPSS software. A significance level of $p < 0.05$ was considered statistically significant. The Shapiro-Wilk test was used to assess the normal distribution of the data for the 30 samples. For normally distributed data, one-way ANOVA was employed to evaluate differences among groups.

RESULTS AND DISCUSSION

Eosinophil Counts

To determine the allergic effect of using cork fish extract hydrogel, rat blood was examined by measuring eosinophil counts, where high eosinophil counts indicate an allergy (normal counts: 1-4%). The test results are shown in Table 1.

Table 1. Eosinophil counts of all treatment groups

Treatment Groups	Eosinophil counts
Cork fish-Hydrogel 15%	1,80 ± 0,84[ab]
Cork fish-Hydrogel 10%	3,00 ± 0,71[bc]
Cork fish-Hydrogel 5%	2,00 ± 0[b]
Bioplacenton	2,20 ± 1,09[b]
Negative Control	4,20 ± 2,17[bc]
Normal (No wound)	0,40 ± 0,55[a]

The Kruskall-Wallis test showed a significant effect between the treatments and the number of eosinophils with a significancies of 0.032 ($p < 0.05$). Duncan's analysis showed significant differences in eosinophil counts between treatment groups. The 15% Cork Fish Hydrogel had an eosinophil count of 1.80 ± 0.84 (superscript 'ab'), not significantly different from the 10% Cork Fish Hydrogel (3.00 ± 0.71bc) and Bioplacenton (2.20 ± 1.09b), but significantly different from the Normal group (0.40 ± 0.55a) which had the lowest eosinophil count. 10% Cork Fish Hydrogel and Negative Control (4.20 ± 2.17bc) had higher eosinophil counts with superscript 'bc' significantly different from 15% Cork Fish Hydrogel and Normal. The 5% Cork Fish Hydrogel (2.00 ± 0b) differed significantly from the Normal group but not significantly from the 15% Cork Fish Hydrogel, Bioplacenton, and Negative Control. The Normal group had the lowest number of eosinophils, significantly different from all other treatment groups, indicating that treatment with cork fish hydrogel and bioplacenton increased the number of eosinophils compared to normal conditions.[34,35]

The results of Spearman correlation analysis showed a significant relationship between eosinophil count and wound diameter shrinkage. The data is shown in Table 2.

Table 2. Correlation between Eosinophil and Wound diameters

		Eosinophil counts	Wound diameter
Eosinophil counts	Pearson correlation	1	0.420
	Sig. (2-tailed)		0.37
	N	30	25
Wound diameter	Pearson correlation	0.420	1
	Sig. (2-tailed)	0.037	
	N	25	25

The Spearman correlation coefficient of 0.420 indicates a moderate and positive relationship, meaning that the greater the number of eosinophils, the greater the wound diameter shrinkage, with a significance of 0.037 ($p < 0.05$).[34,36]

Evaluation of Side Effects

Assessment of side effects was carried out by observing symptoms in the form of changes in the eyes, oral mucosa, skin and fur, seizures, tremors, coma, and death observed after the administration of cork fish extract hydrogel at 24 hours, day 7 and day 15. Observation data on using cork fish extract Hydrogel in rats found that rats' eyes, oral mucosa, skin, and fur were normal. In all treatment groups, convulsions, tremors, coma, and death in rats were not found at 24 hours, 7 days, and 15 days of the study.[37–39]

In terms of allergic effects, we found that there was no erythema and edema in all groups. When calculated based on the primary irritation index, we found that all controls and treatments were categorized as no visible irritation (<2) or non-irritating.[40]

Evaluation of Body Weight

Body weights were taken at the beginning and end of the study to assess changes in body weight, which is an early indicator of the toxic effects of the test samples.[41] Weight loss in animals receiving high doses is generally caused by a decrease in appetite, with the rats' feed intake amounting to 10% of their body weight daily.[42] The data on body weight is presented in Table 3.

Table 3. Body weights of all treatment groups

Treatment Groups	Body weight
Cork fish-Hydrogel 15%	161 ± 3.94^{a}
Cork fish-Hydrogel 10%	170.3 ± 8.20^{a}
Cork fish-Hydrogel 5%	166.4 ± 4.05^{a}
Bioplacenton	172.3 ± 12.32^{a}
Negative Control	164.2 ± 9.05^{a}
Normal (No wound)	169.2 ± 11.26^{a}

The ANOVA test results showed that the treatment did not significantly affect the body weight of Wistar rats, with a significance of 0.365 ($p > 0.05$). The absence of different superscripts indicates that the treatment variation does not significantly affect the body weight of each group.[43]

Observation of Wound Diameter

We evaluated the wound diameter on the 15th day, as presented in Table 4.

Table 4. Wound diameter of all treatment group

Treatment Groups	Wound Diameter
Cork fish-Hydrogel 15%	0.83 ± 0.12-ab
Cork fish-Hydrogel 10%	0.87 ± 0.02^{a}
Cork fish-Hydrogel 5%	0.86 ± 0.15^{a}
Bioplacenton	1.02 ± 0.12^{bc}
Negative Control	1.08 ± 0.08^{c}
Normal (No wound)	-

The ANOVA test results showed a significant effect between treatments and healing of Wistar rats based on wound diameter with a significance of 0.011 ($p < 0.05$). Duncan's analysis showed significant differences in wound diameter between treatment groups.[44] The 15% cork fish hydrogel group had a wound diameter of 0.83 ± 0.12, significantly different from the negative control (1.08 ± 0.08) and bioplacenton (1.02 ± 0.12) but not significantly different from the 10% cork fish hydrogel (0.87 ± 0.02) and 5% cork fish hydrogel (0.86 ± 0.15). The 10% and 5% cork fish hydrogel groups showed no significant difference in wound diameter (0.87 ± 0.02a and 0.86 ± 0.15a), but both significantly differed from the negative control. The bioplacenton group was not significantly different from the negative control but significantly different from the 10% and 5% cork fish hydrogel.

The visual observation of the wound diameter was conducted on days 0, 3, 9, and 15^{th,} as presented in Figure 1.

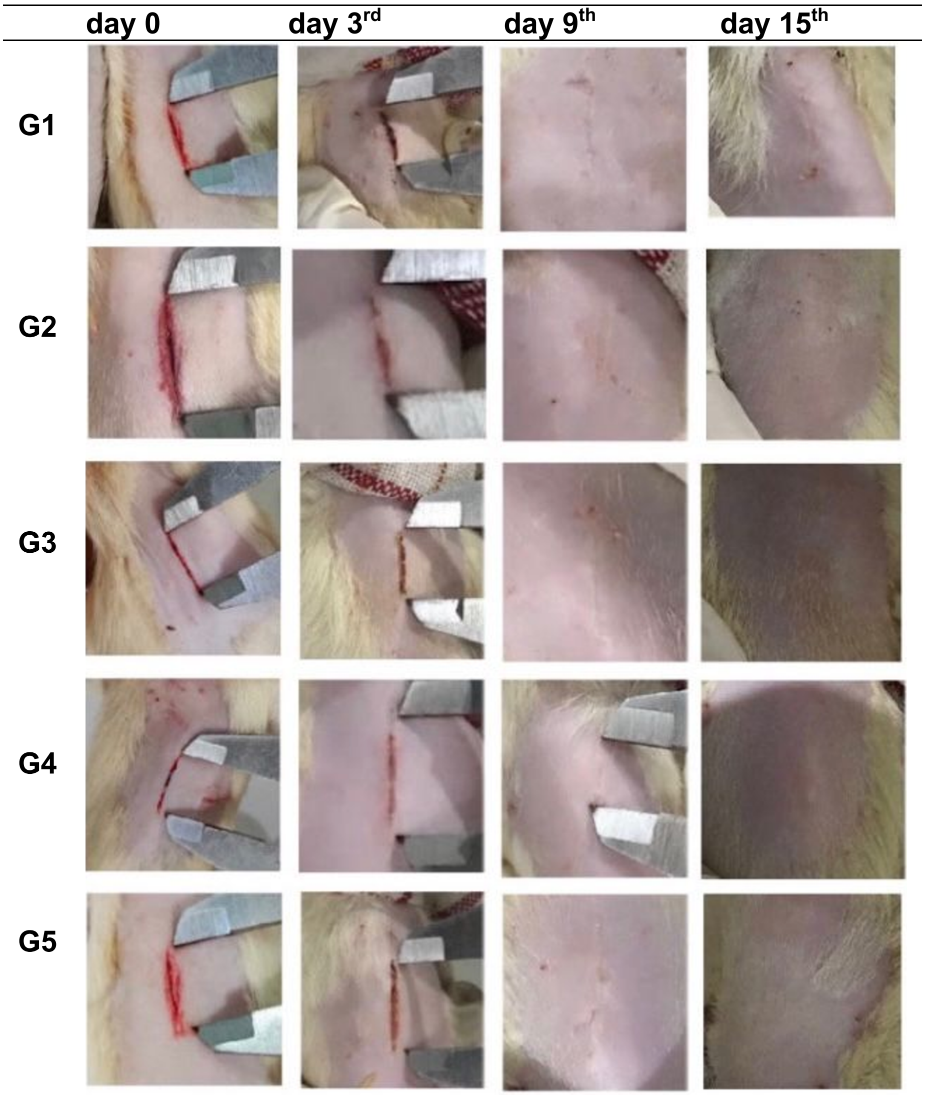

Figure *1*. Progress of wound diameter on the day 0-15th.
***G1: 15%, G2: 10%, G3: 5%, G4: Bioplacenton, G5: Negative control.**

The image illustrates the wound healing process in different groups of male Wistar rats treated with varying concentrations of cork fish extract hydrogel, a positive control (Bioplacenton), and a negative control. Observations were recorded on days 0, 3, 9, and 15, highlighting the progression of wound closure and skin recovery over time.

Day 0: The initial wounds appear fresh, with visible incision lines and no signs of healing. Across all groups (G1 to G5), there is no significant difference in wound condition as this marks the baseline for the experiment.

Day 3: Early healing signs, such as reduced redness and initial scab formation, are observed. Groups treated with cork fish extract hydrogel (G1, G2, and G3) show a more organized wound margin compared to the negative control (G5). The positive control group (G4) also demonstrates a similar healing progression.

Day 9: A significant reduction in wound diameter is evident, particularly in G1 (15% hydrogel), where the wound surface appears more contracted and less inflamed. G2 (10% hydrogel) and G3 (5% hydrogel) also show considerable healing but to a lesser extent than G1. The positive control (G4) displays comparable progress to G1. Meanwhile, the negative control (G5) shows slower healing with persistent redness and unhealed wound margins.

Day 15: Complete healing or near-complete healing is observed in G1, where the wound site is almost indistinguishable from the surrounding skin, indicating the highest effectiveness of the 15% hydrogel. G2 and G3 also show substantial recovery, though small differences in wound closure remain compared to G1. The positive control (G4) exhibits similar outcomes to G1, confirming its efficacy. However, G5 (negative control) still shows incomplete healing, with visible wound traces and less regenerated tissue.

Overall, the progression captured in the image emphasizes the effectiveness of cork fish extract hydrogel, particularly at the 15% concentration, in accelerating wound healing compared to lower concentrations and the negative control. These findings suggest that the hydrogel formulation promotes rapid skin recovery by maintaining a moist wound environment and facilitating tissue regeneration.

The results of this study align with another study, which found that 10% of cork fish extract water-oil phase combination ointment is effective for healing stage II acute open wounds.[45] The nutritional content of the combination ointment is a critical factor in accelerating wound healing, as it is more comprehensive than that of single-phase water or oil ointments. The water phase contains albumin protein, vitamin C, and minerals, while the oil phase contains omega-3 and omega-6 fatty acids. These phases work synergistically in moist conditions to enhance the wound-healing process.[46]

CONCLUSION

The study concludes that 15% cork fish hydrogel is the most effective treatment for subcutaneous wound healing in male Wistar rats, significantly reducing wound diameter compared to the negative control and bioplacenton. The treatment groups showed increased eosinophil counts, correlating with more significant wound shrinkage, as indicated by a moderate positive Spearman correlation. No adverse side effects or allergic reactions, such as erythema or edema, were observed, and the primary irritation index classified all treatments as non-irritating. Additionally, the treatments did not significantly affect the rats' body weight. Overall, cork fish hydrogel, particularly at 15%, enhances wound healing without causing toxicity or irritation.

AUTHORS' CONTRIBUTIONS

Refi Ikhtiari: Supervision, Conceptualization, Data curation, Reviewing.: Nadia Resonia Goviana: Data curation, Investigation, Writing- Original draft preparation.: Fiska Maya Wardhani: Supervision, Methodology, Validation.

ACKNOWLEDGEMENT

None.

FUNDING INFORMATION

No funding was received for this research.

DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author upon reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data results from the author's research and has never been published in other journals.

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