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Yellowfin tuna (*Thunnus albacares*) collagen-based wound dressing promotes wound closure by reducing tissue inflammation

Aree Wanasuntronwong[a], **Pichayamon Maharatanawong**[b], **Nattapon Rotpenpian**[c], **Rudee Surarit**[a,d,*], **Nuttawee Niamsiri**[b,*]

[a] Department of Oral Biology, Faculty of Dentistry, Mahidol University, Bangkok 10400 Thailand
[b] Department of Biotechnology, Faculty of Science, Mahidol University, Bangkok 10400 Thailand
[c] Department of Oral Biology and Occlusion, Faculty of Dentistry, Prince of Songkla University, Songkhla 90110 Thailand
[d] Faculty of Dentistry, Siam University, Bangkok 10160 Thailand

*Corresponding authors, e-mail: rudee.sur@mahidol.ac.th, nuttawee.nia@mahidol.ac.th

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ABSTRACT: This study investigated the wound-closing properties of collagen-based dressings derived from various biological sources. Specifically, we focused on the wound healing process and evaluated the effects of a wound dressing made from collagen derived from the skin of yellowfin tuna. The results demonstrated that the yellowfin-based wound dressing (YCWD) promoted wound healing with good anti-infection properties during the inflammatory phase of the wound healing process. Additionally, the YCWD did not interfere with or negatively impact the natural sequence of events involved in wound healing and promoted complete wound closure. Overall, these findings indicate that the YCWD promoted wound healing and closure with anti-infection effects. These results contribute to current understandings of collagen-based dressings and future potential applications for wound control.

KEYWORDS: yellowfin tuna, intact skin, collagen wound dressing, inflammation

INTRODUCTION

During the wound healing process, injured tissue is replaced with new tissue [1]. The epidermis and dermis of healthy skin form a protective barrier against the external environment. When this barrier is breached, a well-orchestrated series of biochemical reactions are initiated to heal the damage [2]. The normal wound healing process typically consists of several overlapping phases that include hemostasis, inflammation, proliferation, and remodeling [3]. Several factors can affect the wound healing process, especially the size and depth of the wound, the general health of the individual, the presence of underlying diseases, such as diabetes, and external factors, including infections and poor wound care [1]. The inflammatory phase can have both positive and harmful effects. Initially, during the acute phase of wound healing, inflammation is crucial to help clean the wound site, remove debris, and prevent infection [4]. However, persistent and dysregulated inflammation can impede healing of chronic wounds [1].

The wound dressing aids wound contraction and healing [5]. The primary goal of a wound dressing is to provide a temporary physical barrier, absorb drainage, and provide moisture to optimize re-epithelialization [6]. Collagen wound dressings for the management of chronic wounds contain a naturally occurring protein and a critical component of the extracellular matrix (ECM) [5]. These dressings provide a scaffold-like structure that mimics the natural ECM and supports cell migration and proliferation to promote tissue regeneration [6]. Moreover, collagen dressings can help to modulate the inflammatory response by reducing production of inflammatory cytokines such as interleukin-1 and tumor necrosis factor-alpha and promote angiogenesis [6].

Cytoplast™ is a synthetic bioresorbable membrane composed of polytetrafluoroethylene as a physical barrier to protect underlying tissues and promote proper healing for use in dentistry, oral surgery, and guided tissue regeneration procedures [7]. While helpful in certain dental procedures, depending on the dissolution time, Cytoplast™ membranes are not intended for general wound healing applications outside of oral surgery [8].

Piscine and bovine collagen extracts can more effectively promote wound healing than synthetic collagen. Piscine collagen can improve wound closure, increase the production of collagen and other ECM components, and improve the tensile strength of the healed tissue [9]. Similarly, bovine collagen has been shown to accelerate wound healing, promote tissue regeneration, and aid in wound closure [10]. The amino acid composition of piscine collagen generally contains higher amounts of glycine and proline than bovine collagen [9]. Due to the lower molecular weight, piscine collagen is generally more bioavailable than bovine collagen, allowing easier absorption and utilization [9]. This cutting-edge biological wound

dressing consists of intact collagenous fish skin processed into a wound matrix [11]. Notably, piscine collagen is rich in omega-3 fatty acids and naturally resistant to pathogens. The structure of the fish skin wound matrix is surprisingly similar to that of human skin and supports the proliferation of keratinocytes and fibroblasts, which promote healing and the formation of healthy new skin [9]. In addition, high levels of omega-3 fatty acids can contribute to the formation of anti-inflammatory metabolites and a more favorable environment for wound healing [12]. However, an intact matrix of bovine type I collagen with elastin improves the stability and elasticity of the regenerating tissue when used for full-thickness, chronic, and deep dermal burn wounds [13].

Direct comparisons of piscine, bovine, and synthetic collagen-based dressings remain limited because previous studies often examined single collagen sources but not the relative histological effects, wound closure efficiency, or influence on inflammation and tissue regeneration in a controlled setting. Moreover, relatively few studies have investigated broader applications of synthetic membranes, like Cytoplast™, outside of oral surgery.

Therefore, the aim of the present study was to compare the efficacy of piscine, bovine, and synthetic collagen-based dressings on wound closure, inflammatory responses, and histological parameters during the wound healing process in experimental models.

MATERIALS AND METHODS

Chemicals and reagents

Analytical grade chemicals and reagents were used throughout the study. Acetic acid, N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride, glutaraldehyde, and N-hydroxysuccinimide were obtained from Sigma-Aldrich Pte. Ltd. (Singapore). Ethanol and methanol were purchased from RCI Labscan (Bangkok, Thailand). Hydrogen peroxide was sourced from ChemSupply Pty. Ltd. (Gillman, Australia), potassium dihydrogen phosphate from Merck KGaA (Darmstadt, Germany), potassium chloride from BDH Chemicals Ltd. (Poole, England), and sodium chloride from Ajax Chemicals (Cheltenham, Australia).

Preparation of wound dressings

Cytoplast RTMFOAM™, an absorbable collagen-based wound dressing, and intact skin of yellowfin tuna were kindly provided by Thai Union Group PCL (Samut Sakhon, Thailand). Bovine-based and yellowfin tuna-based dressings were fabricated as three-dimensional (3D) scaffolds using the freeze-drying method. In brief, the extracted collagens from bovine tendon and yellowfin tuna skin were dissolved in 0.5 M acetic acid. Then, 100-ml aliquots of the collagen solutions were treated with 0.2 ml of glutaraldehyde crosslinking agent, poured into round molds, cooled at −20 °C overnight, lyophilized in a freeze dryer, washed 3 times with sterile phosphate-buffered saline and sterile deionized water, cooled at −20 °C overnight, and lyophilized again. All collagen-based wound dressings, including Cytoplast RTMFOAM™, bovine-based dressing, yellowfin-based dressing, and yellowfin intact skin, were prepared at a diameter of 2 cm and thickness of 0.3 cm. Finally, the collagen-based wound dressings were sterilized with gamma radiation at 25 kGy.

Scanning electron microscopy (SEM)

The fine structure of each collagen-based dressing was analyzed with a scanning electron microscope (JSM6610LV; JEOL Ltd., Tokyo, Japan). The tested collagens were fixed in 4% glutaraldehyde for 4 h in 0.1 M phosphate buffer, cut along the longitudinal axis using a razor blade, and dehydrated in acetone using a Polaron E3000 critical point dryer (Polaron, Uckfield, UK). The specimens were then mounted on stubs, sputter coated with gold, and viewed under an accelerating voltage of 5 kV.

Experimental protocol

Male Wistar rats ($n = 100$; age, 8 weeks; body weight, 250–350 g) were obtained from the National Laboratory Animal Center of Mahidol University (Nakornpathom, Thailand) and housed in an animal care facility at a constant temperature of 25 ± 1 °C with *ad libitum* access to commercial feed and water. The rats were acclimated to the laboratory environment for 7 days. The protocol of the animal experiments was approved by the National Laboratory Animal Center Animal Care and Use Committee of Mahidol University (approval no. RA2020-37) and conducted in accordance with the ARRIVE (Animals in Research: Reporting *In Vivo* Experiments) guidelines [14] and the Guide for the Care and Use of Laboratory Animals of the National Research Council of Thailand. All care was taken to minimize suffering of the animals.

The animals were randomly assigned to one of five experimental groups: (1) bare wound, (2) Cytoplast™, (3) bovine dressing, (4) yellowfin dressing, or (5) yellowfin intact skin. Data for analysis were recorded on Days 3, 7, 14, 21, and 28.

Excision wound induction and wound dressing application

The animals were anesthetized with 3–4% isoflurane in a ventilated box throughout the wound induction procedure and wound dressing application. The back of each animal was shaved and depilated with antiseptic agents, and a circular (diameter, 2 cm) excision wound was made. Each wound dressing was immersed in sterile water for 2 min and then applied topically to the wound. The treated area was covered with a Tegaderm™ transparent film dressing (3M Company,

Saint Paul, MN, USA). The wound dressing was secured with paper tape, and the torso was wrapped with Coban™ self-adherent wrap (3M Company), followed by Fixumull® transparent adhesive film (3M Company). Animals without wound dressings were used as a control group. Afterward, the rats were allowed to recover in individual cages.

Wound assessment

After removal of the wound dressing, the efficacy of the wound dressing was evaluated using the standard method described by Shah et al [15]. Initially, all securing tapes were carefully removed, and the debris around the wound was gently cleaned. Subsequently, photos that clearly depicted the characteristics of the wound were captured. The wound size was then outlined on a transparent film, measured using a ruler, and recorded (Fig. S1). The wound size (cm^2) was calculated as the length (cm) × width (cm).

At the end of each time point, the animals were anesthetized by carbon dioxide inhalation, and blood was collected by cardiac puncture for hematological analysis. Tissue from the healed wound was also collected from each animal for histological analysis.

Blood collection

Blood samples were collected via cardiac puncture for hematological and chemical analyses. Hematological analysis was performed using an automated analyzer (Procyte Dx™; IDEXX Laboratories, Inc., Westbrook, MA, USA). Cytokine analysis was performed using Bio-Plex Multiplex Immunoassays (Bio-Rad Laboratories, Hercules, CA, USA).

Histopathological analysis of excision wounds

A skin specimen was obtained from the middle of the wound area, preserved in 10% neutral buffered formaldehyde solution for at least 24 h, stained with hematoxylin and eosin (H&E), and examined under a light microscope (516609; Nikon Corporation, Tokyo, Japan). Histological criteria were graded by 3 pathologists as described by Moura Estevão et al [16] and Chen et al [17] (Fig. S2).

RESULTS

Morphology of the collagen-based wound dressing

SEM images of the collagen wound dressing are shown in Fig. 1. Bovine and yellowfin dressings exhibited a regular porous structure with high porosity and various pore sizes. In contrast, an SEM image of the Cytoplast™ dressing showed an irregular porous structure with high porosity. Moreover, the yellowfin intact skin contained fibrous sheets.

Effect of collagen-based wound dressing on the percent reduction of wound size

Progress in the wound healing process was assessed by comparing the percentage reduction in wound size from Day 0 to Days 3, 7, 14, 21, and 28 (Fig. 2). On Day 3, the percentage reduction in wound size was significantly increased in the Cytoplast™, bovine, and yellowfin intact skin groups as compared to the bare wound group. The yellowfin dressing promoted wound healing although there was no significant difference as compared to the bare wound group. On Day 7 onward, there was no significant difference in wound size reduction in the yellowfin and intact fish skin dressing groups as compared to the Cytoplast™ group. By Day 28, the bare wounds and those covered with the yellowfin dressing had completely closed (Fig. 3).

Hematological analysis

The Cytoplast™ and bovine dressings significantly increased red blood cell counts as compared to the untreated wounds ($[F(4,15) = 3.790$, $p \leqslant 0.05$). Conversely, platelet counts and plateletcrit levels were higher with the use of the yellowfin intact skin dressings ($[F(4,15) = 2.053$, $p \leqslant 0.05$ and $[F(4,15) = 1.992$, $p \leqslant 0.05$, respectively) (Table 1).

Cytokine analysis

The application of collagen-based wound dressings tended reduce production of systemic inflammatory cytokines as compared to the bare wound group. However, this reduction in cytokine levels was not statistically significant on Day 14 as compared to the bare wound group (Table 2).

Histopathological analysis

Scab formation was observed in the area of the excision wound in all collagen-based dressing groups (Table 3). However, on Day 28, no scab was observed in the bare wound group ($[F(4,15) = 3.062$, $P = 0.05$).

The pathological scores of the histological sections on Days 3, 7, 14, 21, and 28 are provided in Table 3. On Day 3, fewer inflammatory cells in the wound area were observed in the yellowfin dressing group as compared to the bare wound group. However, on Day 7, more inflammatory cells in the wound were observed in the bovine and yellowfin dressing groups as compared to the bare wound group. On Day 21, a moderate number of inflammatory cells were observed in the wound area of the bovine dressing group. By Day 28, no inflammation was observed in the wound area of the yellowfin dressing group.

Application of the Cytoplast™ wound dressing resulted in the formation of a small new epithelial layer that was more pronounced as compared to the other groups. The application of the Cytoplast™ wound dressing resulted in moderate vascular formation as

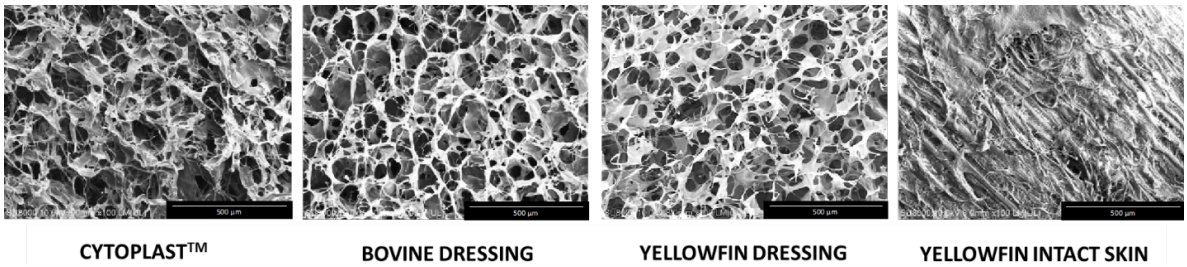

Fig. 1 SEM images (surface views) of the Cytoplast™, bovine dressing, yellowfin dressing, and yellowfin intact skin (magnification, 100×). Scale bar, 500 μm.

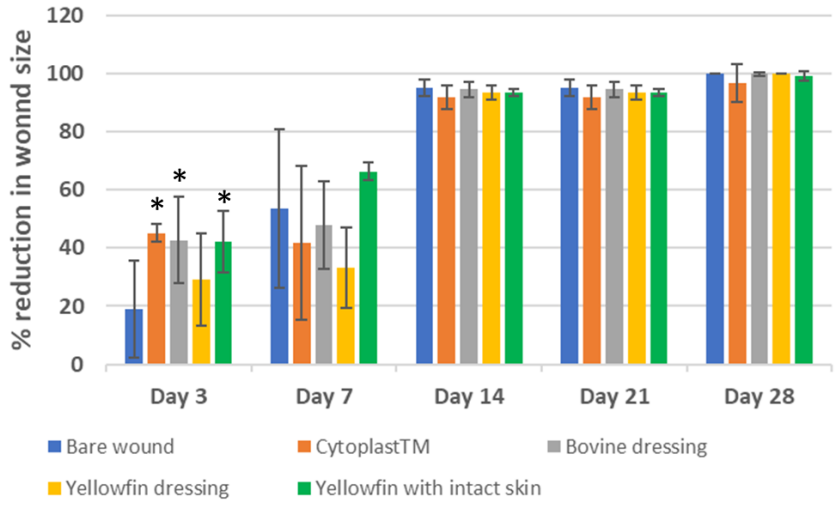

Fig. 2 Percentage reduction in wound size. Data were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's multiple-comparisons test and are expressed as the mean ± standard deviation ($n = 4$). $^*p < 0.05$ vs. the bare wound group.

Table 1 Hematological analysis on Day 3.

Material	RBC (M/μl)	HGB (g/dl)	HCT (%)	PLT (K/μl)	PCT (%)
Bare wound	7.25 ± 0.13	14.33 ± 0.38	44.35 ± 1.04	907.75 ± 49.38	0.63 ± 0.03
Cytoplast™	7.70 ± 0.20*	15.00 ± 0.14	48.95 ± 4.75*	995.50 ± 49.38	0.70 ± 0.09
Bovine dressing	7.91 ± 0.29*	15.40 ± 0.54*	48.35 ± 2.10	939.25 ± 111.66	0.67 ± 0.08
Yellowfin dressing	7.62 ± 0.31	14.88 ± 0.59	46.75 ± 1.84	988.50 ± 46.42	0.69 ± 0.05
Yellowfin with intact skin	7.49 ± 0.28	14.83 ± 0.45	46.10 ± 1.48	1081.75 ± 125.19*	0.78 ± 0.11*

Data were analyzed using one-way ANOVA followed by Dunnett's multiple-comparisons test and are expressed as the mean ± standard deviation ($n = 4$). $^*p < 0.05$ vs. the bare wound group. Abbreviations: HCT, hematocrit; HGB, hemoglobin; PCT, plateletcrit; PLT, platelet count; RBC, red blood cell count.

Table 2 Cytokine analysis on Day 14.

Material	IL-2 (pg/ml)	IL-6 (pg/ml)	INF-α (pg/ml)
Bare wound	61.71 ± 42.81	1.98 ± 1.81	12.56 ± 8.36
Cytoplast™	17.08 ± 8.91	0.78 ± 0.78	12.27 ± 11.73
Bovine dressing	13.74 ± 9.83	1.07 ± 1.02	14.14 ± 6.88
Yellowfin dressing	58.39 ± 39.50	1.23 ± 1.38	18.92 ± 13.12
Yellowfin with intact skin	32.55 ± 57.62	0.52 ± 0.73	8.76 ± 9.70

Data were analyzed using one-way ANOVA followed by Dunnett's multiple-comparisons test and are expressed as the mean ± standard deviation ($n = 4$). Abbreviations: INF-α, interferon gamma, IL, interleukin.

Table 3 Pathological scores of H&E-stained histological sections of excisional rat wounds.

Scab analysis					
	Day 3	Day 7	Day 14	Day 21	Day 28
Bare wound	0.00 ± 0.00	0.67 ± 1.12	1.50 ± 0.58	2.25 ± 0.17	3.00 ± 0.00
Cytoplast™	0.17 ± 0.19	0.25 ± 0.32	1.25 ± 0.50	1.83 ± 0.34	2.17 ± 0.83*
Bovine dressing	0.17 ± 0.34	0.17 ± 0.34	1.33 ± 0.82	1.67 ± 0.67	2.33 ± 0.00*
Yellowfin dressing	0.08 ± 0.17	0.08 ± 0.17	1.17 ± 0.19	1.75 ± 0.50	2.33 ± 0.00*
Yellowfin with intact skin	0.34 ± 0.39	0.25 ± 0.32	1.59 ± 0.42	1.83 ± 0.34	2.25 ± 0.17*
Inflammation analysis					
	Day 3	Day 7	Day 14	Day 21	Day 28
Bare wound	0.17 ± 0.34	1.17 ± 0.58	1.50 ± 0.43	2.67 ± 0.39	2.92 ± 0.16
Cytoplast™	0.59 ± 0.17	1.34 ± 0.39	1.67 ± 0.27	2.59 ± 0.17	2.25 ± 0.17*
Bovine dressing	0.17 ± 0.34	0.17 ± 0.34*	1.50 ± 0.43	1.83 ± 0.58*	2.33 ± 0.00*
Yellowfin dressing	0.75 ± 0.32*	0.42 ± 0.42*	1.42 ± 0.32	2.58 ± 0.32	3.00 ± 0.00
Yellowfin with intact skin	0.17 ± 0.19	0.84 ± 0.19	1.67 ± 0.39	2.58 ± 0.50	2.34 ± 0.39*
Epithelization analysis					
	Day 3	Day 7	Day 14	Day 21	Day 28
Bare wound	0.42 ± 0.32	0.58 ± 0.32	2.34 ± 0.39	2.67 ± 0.27	3.00 ± 0.00
Cytoplast™	0.25 ± 0.32	1.09 ± 0.42*	2.17 ± 0.88	2.25 ± 0.88	2.67 ± 0.67
Bovine dressing	0.34 ± 0.39	0.34 ± 0.39	2.17 ± 0.88	2.17 ± 1.26	3.00 ± 0.00
Yellowfin dressing	0.42 ± 0.32	0.84 ± 0.19	2.17 ± 0.19	2.67 ± 0.27	3.00 ± 0.00
Yellowfin with intact skin	0.58 ± 0.50	1.00 ± 0.00	2.17 ± 0.88	2.75 ± 0.32	3.00 ± 0.00
Neovascularization analysis					
	Day 3	Day 7	Day 14	Day 21	Day 28
Bare wound	1.50 ± 0.64	2.08 ± 0.32	2.67 ± 0.47	2.25 ± 0.17	0.83 ± 0.43
Cytoplast™	1.42 ± 0.50	2.08 ± 0.17	2.83 ± 0.58	1.17 ± 0.58	2.00 ± 0.27*
Bovine dressing	1.75 ± 0.50	2.34 ± 0.61	2.67 ± 0.27	2.17 ± 0.84	1.17 ± 0.57
Yellowfin dressing	1.50 ± 0.20	2.67 ± 0.39	2.75 ± 0.32	1.67 ± 0.61	1.00 ± 0.47
Yellowfin with intact skin	1.33 ± 0.27	2.58 ± 0.50	2.59 ± 0.63	1.17 ± 0.88	1.42 ± 0.69
ECM deposition analysis					
	Day 3	Day 7	Day 14	Day 21	Day 28
Bare wound	3.00 ± 0.00	2.33 ± 0.72	1.83 ± 0.34	2.67 ± 0.39	0.00 ± 0.00
Cytoplast™	2.33 ± 0.00*	2.25 ± 0.42	1.92 ± 0.79	1.08 ± 0.17*	0.92 ± 0.50*
Bovine dressing	2.92 ± 0.17	2.75 ± 0.32	1.50 ± 0.43	1.25 ± 0.32*	0.08 ± 0.17
Yellowfin dressing	3.00 ± 0.00	2.84 ± 0.19	1.42 ± 0.32	1.67 ± 0.47*	0.17 ± 0.34
Yellowfin with intact skin	3.00 ± 0.00	2.84 ± 0.19	1.92 ± 0.17	1.25 ± 0.32*	0.34 ± 0.39
Collagen density analysis					
	Day 3	Day 7	Day 14	Day 21	Day 28
Bare wound	2.92 ± 0.17	2.08 ± 0.32	1.58 ± 0.74	2.67 ± 0.27	0.00 ± 0.00
Cytoplast™	2.33 ± 0.00*	2.42 ± 0.42	1.42 ± 0.42	0.50 ± 0.34*	1.33 ± 0.67*
Bovine dressing	2.83 ± 0.34	2.25 ± 0.17	0.83 ± 0.43*	1.09 ± 0.63*	0.83 ± 0.64*
Yellowfin dressing	2.84 ± 0.19	2.67 ± 0.39*	1.33 ± 0.27	0.33 ± 0.47*	0.83 ± 0.34*
Yellowfin with intact skin	2.92 ± 0.17	2.58 ± 0.32	1.42 ± 0.17	0.25 ± 0.17*	0.58 ± 0.32

Data were analyzed using one-way ANOVA followed by Dunnett's multiple-comparisons test and are expressed as the mean ± standard deviation ($n = 4$). * $p < 0.05$ vs. the bare wound group.

compared to the bare wound group. On Day 3, application of the Cytoplast™ wound dressing accelerated accumulation of fibroblasts in the wound area as compared to the other groups. On Day 21, incomplete presence of ECM was observed in all wound dressing groups as compared to the bare wound group. On Day 28, ECM deposition was lower in the Cytoplast™ group as compared to the other groups.

On Day 3, there was a significant difference in the moderate collagen recovery score of the Cytoplast™ group as compared to the other groups. On Day 7, collagen recovery was less evident in the yellowfin-based wound dressing group as compared to the other groups. On Day 14, collagen restoration was greater in the bovine dressing group than the other groups. On Day 21, collagen recovery was higher in all dressing groups as compared to the bare wound group. On Day 21, collagen recovery was lower in the Cytoplast™,

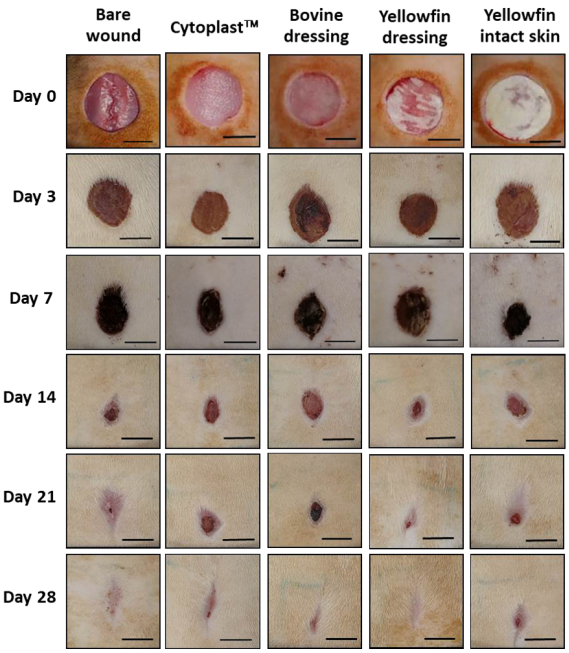

Fig. 3 Extent of wound healing on Days 3, 7, 14, 21, and 28 for the bare wound, Cytoplast™, bovine dressing, yellowfin dressing, and yellowfin intact skin groups. Scale bar, 1 cm.

bovine, and yellowfin dressing groups than the intact fish skin and bare wound groups.

DISCUSSION

In this study, different types of collagen-based dressings were used to guide wound closure, and the effectiveness of the dressing was compared. Yellowfin dressings completely closed the wound surface as compared to other dressings. From Day 7 onward, there was no statistical difference in wound size among the groups, demonstrating that the piscine-based collagen dressing promoted wound healing.

Wound healing is a dynamic and complex process that involves a series of precisely coordinated phases: coagulation, inflammation, proliferation, and remodeling [3]. These phases overlap and interact to promote efficient wound healing.

As an essential step in the wound healing process, the primary goal of the coagulation phase is to promote blood clot formation to prevent further bleeding and provide a temporary barrier at the wound site. However, excessive or prolonged blood clotting and scab formation can affect the subsequent phases of the wound healing process. While the initial formation of a blood clot is crucial to control bleeding and provide a temporary barrier, prolonged clotting and excessive scab formation can hinder the healing process. Systemic blood analysis showed no significant alteration in hematocrit and platelet count between the yellowfin dressing and bare wound groups, indicating that the dressing had no noticeable effect on these blood parameters. Additionally, the absence of a significant difference in scab formation and the percent reduction of wound size between the 2 groups further supports the conclusion that the yellowfin dressing does not impede the coagulative process of wound healing. These parameters are important indicators of the healing process, and the lack of difference suggests that the dressing did not negatively impact wound closure or healing progression. Interestingly, intact yellowfin skin enhanced platelet levels. Notably, the red blood cell count and hemoglobin were slightly increased in the bovine and Cytoplast™ dressing groups, suggesting acceleration of the coagulation phase and these wound dressings are particularly suitable for wounds lacking a robust coagulation phase, such as chronic and burn wounds.

The late coagulation phase overlaps with the initial inflammatory phase. Interleukin-2, interleukin-6, and interferons play intricate roles in wound healing by modulating the immune response, inflammation, and tissue repair processes. Systematic blood analysis showed no difference in cytokine levels between the yellowfin dressing and bare wound groups, suggesting that the dressing did not significantly affect the production or release of cytokines, which are important signaling molecules involved in the inflammatory response. Histological analysis also revealed no significant differences in scab formation, epithelialization, and neovascularization between the yellowfin dressing and bare wound groups on Days 7 and 14, indicating that the dressing had no noticeable impact on these aspects of wound healing. However, it is worth noting that the yellowfin dressing group exhibited slightly more inflammation than the bare wound group on Day 7 but returned to normal levels by Day 14. This transient increase in inflammation could be due to the dressing interacting with immune cells, such as neutrophils and macrophages, which are involved in the early inflammatory response. The presence of a slightly heightened inflammatory response on Day 7 suggests that the yellowfin dressing may enhance the wound cleansing process by facilitating the removal of debris, bacteria, and dead cells [4]. This could be beneficial to protect the wound from infection during the initial stages of healing.

The proliferation and remodeling phases are a continuous process following the inflammatory phase and are characterized by the proliferation and migration of various cells involved in tissue repair and regeneration. The yellowfin dressing, similar to other collagen-based dressings, has been shown to promote re-epithelialization in *in vitro* studies [18]. Importantly, no toxicity was observed following gamma irradiation during the product preparation process [19], supporting its safety for clinical application. In addition to these findings, the yellowfin dressing demonstrated

significant effects on extracellular matrix (ECM) remodeling and increased collagen density compared to the bare wound group. These results suggest its potential efficacy in enhancing wound healing. The higher density of the extracellular matrix and collagen suggests increased deposition and organization of these components, which are crucial for tissue repair and regeneration [1, 2]. The ECM provides a structural framework for cells and tissues, facilitates cell migration, and plays a role in wound contraction. Collagen, as the main component of the ECM, contributes to the strength and integrity of the healing wound [1, 2]. Therefore, the higher density of the extracellular matrix and collagen suggests improved tissue organization and support for cell proliferation and migration, which are essential processes during the proliferation phase of wound healing [1, 2].

The results clearly demonstrated that yellowfin tuna dressing and yellowfin intact skin could be used to promote wound healing, as confirmed by the reduced wound size, lack of toxicity, hematological findings, and histopathological results. The use of piscine collagen could lower the cost of production since this dressing can be produced from leftover parts of fish, which usually have no commercial value. The price of this dressing may be lower than commercially available wound dressings produced from bovine collagen. Moreover, the use of piscine collagen is not prohibited based on religion.

There were several limitations to this study that should be addressed. First, the relatively small number of animals used in this study may limit the statistical power and generalizability of the findings. Larger sample sizes are recommended in future studies to validate the observed effects and ensure more robust conclusions. Second, this preliminary investigation was conducted with a controlled animal model, which may not fully replicate the complexity of human wound healing, especially for immunocompromised patients. Third, a longer follow-up period is necessary to evaluate scar formation, tensile strength, and long-term tissue remodeling. Fourth, although systemic inflammatory markers were assessed, localized cytokine expression and molecular signaling at the wound site were not measured, which limits clarification of the underlying mechanistic pathways. Fifth, cytokine release was assessed on Day 14, which may be in the late state of inflammation. Therefore, an earlier time point is needed to clarify the state of inflammation.

Clinical implications and future studies

These findings suggest that collagen-based wound dressings derived from yellowfin tuna may support wound healing as effectively as traditional options, with potential advantages in platelet activation and ECM formation. The biocompatibility and efficacy in promoting tissue regeneration highlight their promise as cost-effective, marine-based alternatives to mammalian collagen dressings. These dressings may be particularly beneficial in settings with limited access to conventional wound care materials or for patients with sensitivities to bovine- or porcine-derived products.

Future studies should aim to validate these findings in clinical trials involving human subjects, particularly patients with systemic diseases, such as diabetes or vascular disorders that impair wound healing. Molecular investigations into the specific bioactive compounds present in yellowfin collagen and potential roles in modulating inflammation and regeneration are also warranted. Moreover, evaluating the mechanical properties and biodegradability of the dressings over time would help optimize formulation for clinical use.

CONCLUSION

Overall, these results suggest that the yellowfin dressing can facilitate complete wound closure due to potential anti-infection properties during the early inflammatory phase. The yellowfin tuna collagen-based wound dressing also promoted wound healing without acute or prolonged cytotoxicity.

Appendix A. Supplementary data

Supplementary data associated with this article can be found at https://dx.doi.org/10.2306/scienceasia1513-1874.2025.076.

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Appendix A. Supplementary data

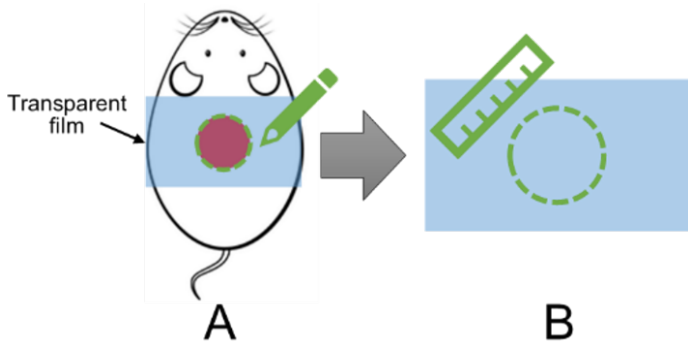

Fig. S1 Measurement of wound size on transparent film (A) with a ruler (B).

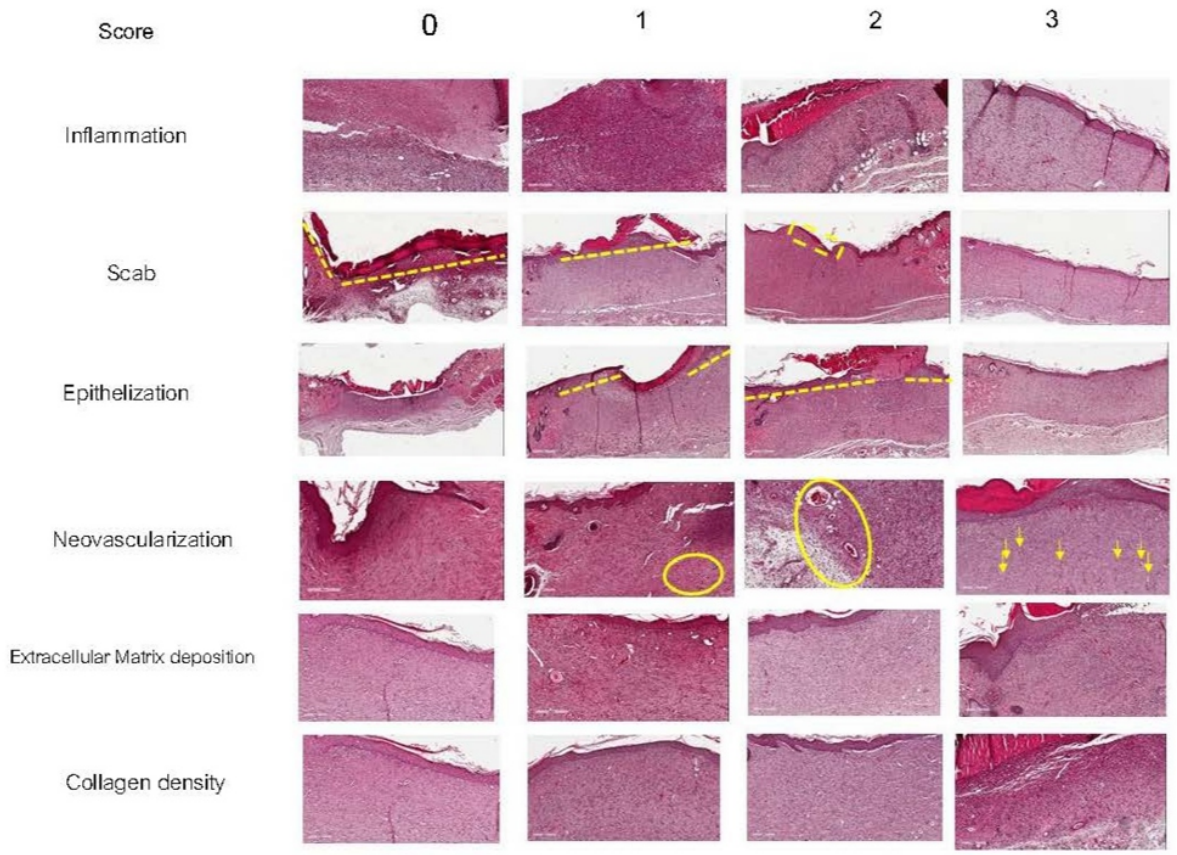

Fig. S2 Histological scoring criteria for wound healing adapted from de Moura Estevão et al [16] and Chen et al [17]. Scab formation and inflammation were scored as 0 = severe, 1 = moderate, 2 = discrete, or 3 = absent. ECM deposition, collagen density, and vascularization were graded as 0 = normal skin, 1 = mild, 2 = moderate, or 3 = severe. Epithelialization was scored as 0 = absent, 1 = discrete (< 1/3 wound gap), 2 = moderate (> 1/3 wound gap), or 3 = complete (normal skin).