Fish Skin as an Alternative Biological Wound Dressing in the Wound Healing Process

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Abstract

Introduction: The benefit of previous knowledge and recent studies is important in accelerating and improving the quality of difficult and chronic wounds.

Biological coatings are one of the most effective solutions today. That’s why tissue engineering specialists are always looking for safe and inexpensive biological coatings.

Another solution is the allograft. Allografts are preferred as temporary coatings on the wound, but because of religious, cultural, and traditional beliefs and also the possibility of transmitting contagious diseases such as hard to heal viral diseases and prion diseases limiting the use of this type of biological material. On the other hand, they are very expensive to prepare and use.

In recent years, the use of animal resources has been used as an alternative to the production of biological bandages called zoografting. In this method, the skin of many animals, including poultry, rats, pigeons, dogs, cats, frogs, calves, cows and pigs, has been studied as a biological cover in the process of wound healing.

The use of animal skin has led to problems ranging from transmission of common human and animal diseases (zoonosis) such as FMD, avian and porcine influenza, endogenous porcine retrovirus, and bovine spongiform encephalopathy to elicit immunologic responses from the recipient.

In addition, the use of aquatic resources as a temporary biological coating has been approved by several researchers worldwide.

Purpose of Study: The purpose of this study is to review the characteristics of fish skin in terms of structure, biodegradability, thermal, elastic and microbial resistance, protein and fatty acid content, as well as its biocompatibility for use in temporary biological dressing and its efficiency in human wound management.

Method: This article is a review of scientific papers and case reports, collects, and integrates them.

Conclusion: Fish skin is a rich source of amino acid and protein content, especially collagen type I and is expected to increase keratinocyte differentiation and migration and accelerate the proliferation of epithelial cells.

Due to the abundant presence of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) in fish skin and their anti-inflammatory effect, reducing the process of inflammation in wound healing as well as reducing pain in the patient can help accelerate this process.

Fish skin, because of its structural similarity to human skin and the limited immune responses to it and the antimicrobial activity in its amino acid contents, can be well used as biomass for wound healing in humans.

On the other hand, since fish skin is a waste in the aquaculture industry, and because it is much easier and less costly to prepare it in bio-coatings, it can be economically feasible.

Keywords: Fish Skin; Tilapia Skin Graft; Wound Healing; Zoografting; Xenograft; NTFS Graft

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**Abbreviations**

EGF: Epithelial Growth Factor; FGF: Fibroblast Growth Factor; MMP-9: Matrix Metallopeptidase 9; TGF-B1: Transforming Growth Factor Beta 1; TP3: Tilapia Piscidine 3; TP4: Tilapia Piscidine 4; VEGF: Vascular Endothelial Growth Factor; EPA: Eicosa Pentaenoic Acid; DHA: Docosa Hexaenoic Acid; AMP: Anti Microbial Peptide; NTFS: Nile Tilapia Fish Skin; DPTB: Deep Partial Thickness Burn

**Introduction**

The process of wound healing is a complex and coordinated set of physiological and biological events and the process accelerating is one of the main goals. Today, the biologic wound dressing includes both intrinsic (allograft) and extrinsic (xenograft) transplants that have received special attention [1-6]. Allografts including human (or cadaver) skin grafts, allogeneic amniotic membranes, and xenografts consist of natural (such as animal skin), synthetic and semi-synthetic grafts [5,7,8]. Although allografts are preferred as temporary wounds cover, its usage would be impossible due to many issues including religious beliefs, cultural and geographical affairs as well as the possibility of transmitting contagious diseases and the high cost of preparation [7-14]. In various studies, different types of animal skins have been used as biological bandages, including cats, poultry, cows, dogs, frogs, lizards, pigs, pigeons, rabbits, sheep, rats and bullfrog [7,8,13,15-17]. Meanwhile, the use of aquatic resources as a temporary biological coating in the wound healing process has been recommended by many researchers worldwide [18,19].

**Materials and Methods**

This article is a review of scientific papers and case reports, collects, and integrates them.

**Results**

**Collagen**

Fish skin collagen is the major structural protein in the extracellular matrix that is easier to access and lower cost than mammalian origins significantly induces expression of EGF and FGF, which can promote proliferation and differentiation of fibroblasts, keratinocytes migration, and regulation of involucrin, filaggrin, MMP-9, Tgase 1 and TGF-B1 gene expression [2,8,11,20-24].

**Amino acid content of fish skin collagen**

Aquatic collagen hydrolysis materials, especially Nile tilapia (*Oreochromis niloticus*), have a particular ability to induce cellular differentiation, due to the diverse amino acid content consist of glycine, proline, and hydroxyproline, that are the majority of them. Collagen extracted from aquatic sources has limited tyrosine and methionine. Proline and tyrosine play important roles in regulating keratinocyte migration (HaCaT) and differentiation, and methionine plays a key role in the synthesis of proteins and nucleic acids, thus managing cell proliferation and differentiation [3,9,11,22-24].

Anti-inflammatory, antibacterial, antioxidant, Anti-hypertensive, nerve-protecting, anti-aging activities and enhances granulation tissue formation are the another aquatic collagen peptides properties.

The sequences of arginine, glycine and aspartic acid amino acids as the main peptides are involved in the intrinsic adhesion of cells.

Also, these sequences playing a key role in the functional parts of proteins such as vitronectin, fibrinogen, laminin, tenascin, von Willebrand factor and osteopontin [3,20,26-28].

Fish collagen peptides promote post-transcriptional changes in collagen maturation and gene expression for cell differentiation in osteoblastic cells.

Also, nanofibers made from fish skin collagen, especially tilapia, significantly stimulate re-epithelialization and can also stimulate cell adhesion and proliferation due to their hydrophilic properties.

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Healing stimulant peptides
There is a particular type of piscidin in the tilapia fish skin (tilapia piscidin-3 or TP3) that accelerates the progress of proliferation, remodeling, and maturation of infected wounds. Tilapia piscidin-4 or (TP4) in Nile tilapia collagen, stimulates cell proliferation and activation of EGF, TGF, and VEGF [3,24,29-31].

Fatty acid content
One of the most important fatty acids found in fish skin is unsaturated omega-3 fatty acids, including EPA and DHA, have antiviral and antibacterial properties, which make it an antimicrobial barrier to the wound site. Omega-3 decreases inflammatory responses by reducing pro-inflammatory cytokines migration through the endothelium. The benefits have been repeatedly confirmed in diabetic wound healing [18,32,33-38].

Microbial properties
Microbial flora
Fish skin contains non-infectious microbiota that is not infectious even without sterilization process [2,8,39,40].

Antimicrobial compounds
Omega-3
The antimicrobial properties of omega-3 fatty acids make fish skin protective against germs [18,32-38].

Antimicrobial peptides (AMPs)
The presence of several AMPs in fish skin has been dedicated to extensive activity against pathogenic bacteria, fungi, viruses as well as parasites [3,24,29-31,41-44].

Adherence
The good graft adhesion significantly prevents the mechanical penetration of germs into the wound (48 to 72 hours max) [5,7-9,11,18,45].

Immunogenicity stimulation
AMPs stimulate cellular immunity along with those immunogenicity. Whereas TP3 directly kill pathogens, reduces infectious inflammatory reactions with no significant changes in biochemical and hematological factors [29,43,46].

Biocompatibility
The lower content of aromatic amino acids in fish skin made it highly adapted to human skin and other mammals [9,11,22,47].

Discussion
The good graft adhesion to the wound bed and no need for replacement increase patient well-being reduced the need for anesthetics and analgesics (Both in terms of cost and side effects), hospitalization, and the workload of medical staff [2,7,8,45,48,49].

On the other hand, these grafts accelerating the healing process due to free from healing delaying factors such as pain, stress, and itching [3,7,8,49,50]. Despite promising and effective tissue engineering strategies, they can not be exploited in low and middle-income countries.
Figure 1A: A 3-year-old boy presented at our burn treatment center with scalds on the left side of the face, neck, anterior thorax, abdomen, and left arm.

Figure 1B: The appearance of the wound after removal of necrotic tissue and blisters, an essential step to allow maximal contact between the tilapia skin and the wound bed.

Figure 1C: The appearance of the wound after tilapia skin application to the anterior thorax, abdomen, and left arm.

Figure 1D: On the sixth day of treatment, the dressing prepared with tilapia skin was opened for the first time. Good adherence of tilapia skin to the wound bed was detected.

Figure 1E: The appearance of the wound after removal of tilapia skin, with a total of 10 days required for the complete re-epithelialization of the patient’s superficial partial thickness burn.

Figure 1F: A final visit of the patient to the burn unit 1 week after the day of dressing removal was performed, allowing for Post-treatment register of the wound appearance.

Figure 2: Deep partial thickness burn in the left upper limb, after cleaning of the lesion [2].
Figure 3: The appearance of the left upper limb after NTFS application [2].

Figure 4: The appearance of the left upper limb lesion after removal of NTFS, with a total of 17 days required for complete reepithelialization of the DPTB [2].

Conclusion

Fish skin rich in amino acid and protein content, omega-3 fatty acids and structural similarity to human skin, making it possible to use as a biological coating for wound healing in humans. These grafts are much easier and less costly to fabricate than other tissue engineering procedures.

Conflict of Interest

The authors declare no conflict of interest.

Bibliography


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