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Review Article

Accelerated Regeneration of Human Skin using Acellular Fish Skin Grafts: A Comprehensive Review

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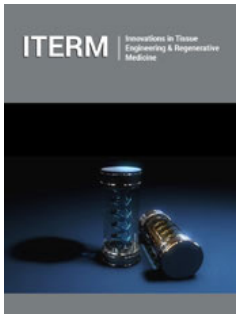

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Abstract

The quest for effective wound healing strategies has led to the exploration of novel biomaterials, with acellular fish skin grafts emerging as a promising solution for accelerating the regeneration of human skin. This comprehensive review provides an in-depth analysis of the scientific literature surrounding the application of acellular fish skin grafts in wound care and tissue regeneration. Drawing upon evidence from experimental studies, clinical trials, and mechanistic investigations, the review elucidates the structural, biochemical, and immunomodulatory properties of fish skin that contribute to its efficacy as a biomimetic scaffold for skin regeneration. Through a synthesis of key findings, the review highlights the diverse applications of acellular fish skin grafts in promoting accelerated wound healing, reducing scar formation, and enhancing tissue regeneration across various acute and chronic wound conditions. Furthermore, the review discusses ongoing research efforts aimed at optimizing graft design, manufacturing processes, and clinical delivery methods to maximize therapeutic outcomes and ensure widespread accessibility of fish skin-derived products. By offering insights into the potential of acellular fish skin grafts to revolutionize wound care and tissue engineering, this review underscores their significance as a transformative approach in the field of regenerative medicine.

Keywords: Acellular fish skin grafts; Chronic wounds; Xenograft; Tissue regeneration; Wound healing

Introduction

The skin, the largest organ in the human body, acts as the first line of defense by acting as a barrier to harmful foreign particles and organisms. Thus, any damage or disruption to the structural integrity of the skin, via cuts, tears or punctures allows entry of pathogens and the wound becomes susceptible to infections. Wound infection typically results in arrest of the skin healing process in the inflammatory stage as well as formation of biofilms occur, which delay healing of the cutaneous and subcutaneous layers. Apart from pathogenic infections, certain conditions can also lead to chronic inflammation of wounds, such as diabetes or hypersensitivity to materials involved in wound treatment. Burn wounds constitute a major cause for skin damage, being statistically ranked in the fourth position worldwide in the leading causes of dermal wounds [1]. Burns sorely affect the layers of the skin sometimes being fatal resulting in around 300,000 deaths globally [1,2]. If left unchecked, such chronic wounds can fester and lead to severe complications [3].

Skin injuries, whether resulting from trauma, burns, or chronic wounds, pose significant challenges to healthcare systems worldwide due to their detrimental impact on patient well-being and quality of life. Traditional approaches to wound management often fall short in promoting efficient and aesthetically pleasing healing outcomes. Traditionally, in the case of deep dermal and full-thickness injuries, treatment is done by application of split-thickness skin autografts. Although autografts are the accepted gold standard for such treatments, it is often not possible in the case of extensive damage resulting in the absence of adequate

donor skin. At these times, treatment is usually done by application of cadaver allografts or porcine xenografts [1,2]. However, both pose the risk of transmission of potentially harmful pathogens and/or possible graft rejection. Thus, there is a tremendous need for alternative products, such as cell or tissue-based products (CTPs) which can be used instead of grafts and can enhance wound healing and overcome donor site morbidities by incorporating seamlessly into host tissue matrix.

Recent advancements in biomaterial science have led to the exploration of novel strategies for tissue regeneration, with acellular fish skin grafts emerging as a promising solution. Drawing inspiration from nature's inherent regenerative capabilities, acellular fish skin grafts offer a unique combination of structural, biochemical, and immunomodulatory properties that facilitate accelerated wound healing while minimizing scar formation and inflammatory responses. Acellular Fish Skin (AFS), sourced from the Atlantic cod (*Gadus morhua*) or the Nile Tilapia (*Oreochromis niloticus*) is a naturally derived biomaterial which shows great potential as a favorable skin regenerating CTP, with little to no risk of transmission of pathogens, faster healing times, providing antimicrobial properties and ease of manufacturing compared to other conventional CTPs, such as Fetal Bovine Dermis (FBD), porcine intestinal submucosa or dehydrated amnion chorionic membrane [2,3].

Sourcing and Manufacturing

Acellular piscine skin xenografts are mostly sourced from the Atlantic cod (*Gadus morhua*), with some other species such as the Nile Tilapia (*Oreochromis niloticus*) also showing similar potential [4]. The fish skin is decellularized using osmotic manipulation and a detergent, such as sodium dodecyl sulphate, followed by decalcification using nitric acid [5], as unlike xenografts from other sources, piscine skin need not be subjected to harsh chemical treatment for possible pathogenic inactivation, owing to their marine ecosystem preventing such microbial growth. Thus, it results in the retention of useful bioactive components such as omega-3 polyunsaturated fatty acids and collagen structures, which expedite the dermal healing process, while also lowering production costs and adverse environmental effects [6]. Unlike allogenic split-thickness skin grafts, which can experience graft rejection as late as 25 years later after application [7], decellularized fish skin grafts show a remarkably high level of biocompatibility with human skin tissue and show no toxicity or unwanted hypersensitivity upon application [1,6]. Moreover, acellular fish CTPs have an excellent shelf life, maintaining effectiveness up to 3 years from manufacture [8] The use of an effective and minimally destructive manufacturing process, low risk of pathogen transmission and an extended shelf life are all excellent traits for a medical CTP, with high potential for marketability and use in adverse environments (Figure 1).

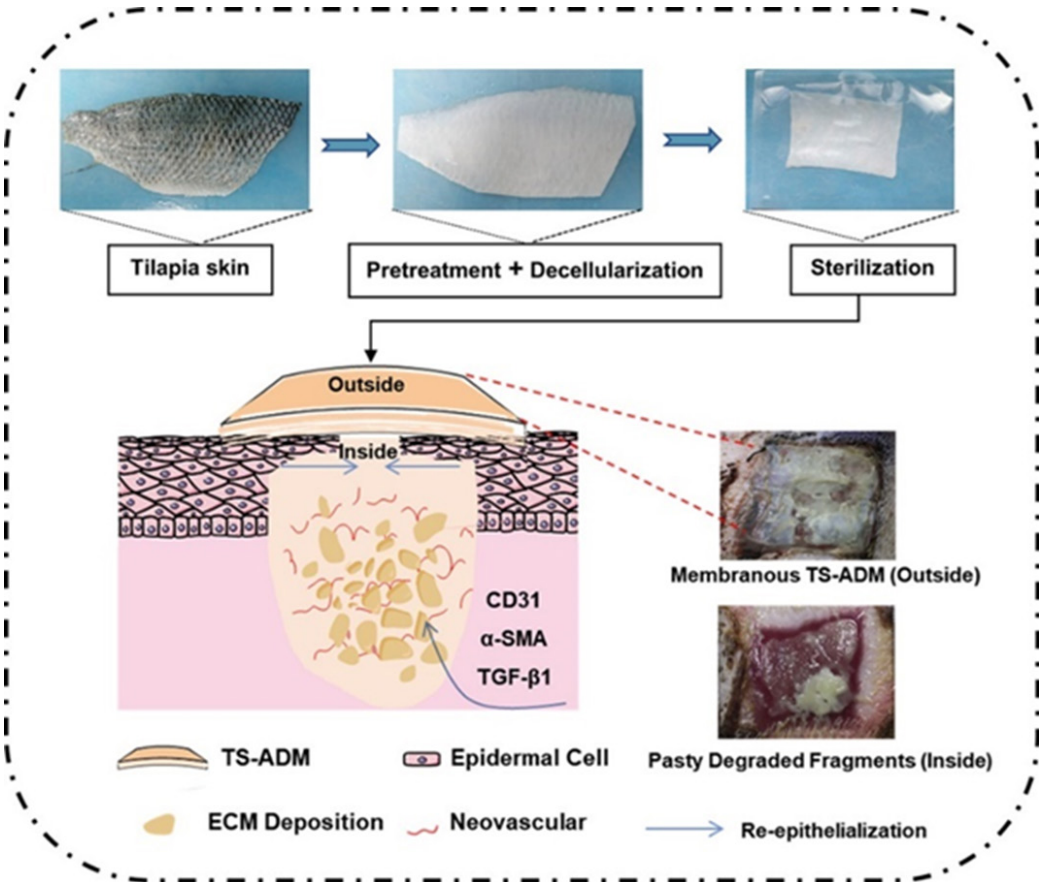

Figure 1: Schematic diagram demonstrating the manufacture of piscine Acellular Dermal Matrix (ADM) and its role in promoting extracellular matrix deposition, angiogenesis and re-epithelialization by forming a microenvironment conducive to the expression of TGF-β1, α-SMA and CD31 [9].

Mechanical Properties

The Atlantic cod has 3 layers on its skin: an epidermis, an intermediate layer, and a basal layer, which show remarkable similarity to human skin. The fish skin has a porous structure containing 16.7 holes per 100μm^2 on average and is made up of a matrix of type I collagen, which can effectively bind to the cytokines present in the human body [1-9]. Alongside similarities in macrostructure of piscine CTPs to human skin, they also provide a suitable microstructure for the penetration of native human cells and compounds. A study by Bružauskaitė et al. [10] demonstrated that xenograft pores must be smaller than 160μm to allow optimal growth and attachment of human skin fibroblasts. Moreover, migration of human fibroblast cells is inhibited by membranes of pore diameter <1μm [10]. Meanwhile, Atlantic cod skin has a pore diameter of 16.1μm and never falls below 1μm , thus providing an excellent scaffold for human skin fibroblasts to penetrate and proliferate to a far greater degree than other conventional xenografts [3]. Furthermore, this collagen matrix has proline incorporated into it, improving its physical and thermal stability, which contributes to its long shelf life [11]. Thus, fish skin CTPs are able to closely mimic native human tissues and provide a familiar macro and microstructure for the attachment, penetration and proliferation of human cells in them, facilitating a better rate of tissue regeneration and wound healing (Figure 2).

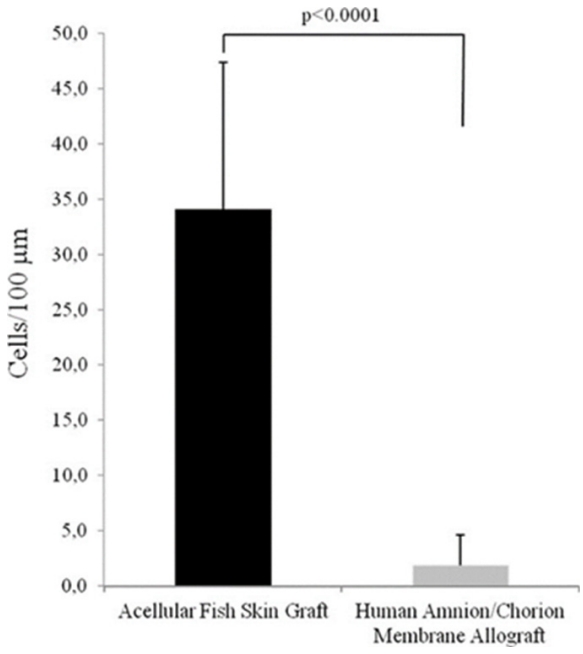

Figure 2: Comparison of cellular ingrowth into acellular fish skin graft against human amnion/chorion membrane allograft, showing significant difference [1].

Biological Properties

Piscine CTPs have a unique lipid profile, being rich in omega-3-fatty acids, which imparts anti-inflammatory and anti-microbial properties to the graft, while also encouraging in-growth of host cell and adipose stem cell [12]. In contrast, cadaver grafts contain greater concentrations of omega-6-fatty acids. The fast-healing effects of piscine grafts were demonstrated by a significantly fast wound closure time when compared to porcine intestinal derived matrices [1]. Moreover, omega-3-PUFAs have also shown also to help in mitigating subject pain by inhibiting neurosensory pathways by activating microglia, leading to a reduced release of pro-inflammatory cytokines, such as TNF-α [13]. This property eliminates the need for analgesic medications and promote accelerated wound healing in chronic cases. Recent studies have demonstrated the role of two omega-3 derived lipid mediators, resolvins and protectins, in imparting anti-inflammatory and anti-microbial properties. These compounds are hydroxylated derivatives of Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA) [13], both of which are found in high concentrations in piscine CTPs.

Acellular fish skin grafts have the advantage of excellent biocompatibility and absorbability as the matrix allows a great level of cellular infiltration and remodelling. This, coupled with a slow degradation time, promotes autologous cell infiltration [3]. A study by Magnusson et al. [12] demonstrated no allergic reaction to the xenograft, possibly because a major fish allergen parvalbumin is found in fish flesh and not in fish skin [12]. Thus, acellular fish skin grafts can be administered to patients with a history of severe hypersensitivity to foreign substances.

Applications

Treatment of burn wounds

According to a study by the World Health Organization,11 million burn wound cases occur annually, with over 180,000 cases being fatal [14], while nonfatal cases are associated with disfigurement, disability, prolonged pain and suffering. Burn wound healing and management continues to be a major challenge for victims and the health care sector, resulting in tremendous socio-economic stress, especially in low and middle-income countries. A study by Saavedra et al. [15], aimed at exploring the costs in burn wound hospital care around the world, found out the mean cost of treatment per burn patient to be within US$ 10.58 to US$ 125,597.86, depending on wound severity, complications and other socio-economic factors [15]. Burn wound healing time stands as the major factor for the possibility of development of complications, as infections are the leading cause of death in burn patients [4]. There are various ways for the treatment of burn wounds, depending on the extent and severity of damage, such as collagen alginate dressings, silver sulphadiazine cream 1%, and various forms of skin grafts (autografts, allografts and xenografts), all of which protect damaged tissue and promote re-epithelization. However, usage of collagen alginate and silver sulphadiazine cream 1% requires frequent dressing changes, making them highly inconvenient for both patients and medical personnel [16].

For Superficial Partial-Thickness Burns (SPTB), the standard medical protocol involves the use of autograft from alternate donor sites from patient's body, due to its high biocompatibility and no fear of graft rejection. However, that is not possible in the case of extensive burn damage with limited donor skin availability [17]. For such cases, allografts taken from donors of the same species, typically cadaver skin, can be employed as a temporary

dressing. Cadaver skin can be made free of antigenic components by lyophilization followed by gamma irradiation, with human trials confirming no immunogenic reaction after application [18]. However, even after such high standards of quality control, cadaver skin still possesses a significant risk of transmission of diseases and pathogens, on top of increasing costs due to the myriad safety protocols involved in sterilization and manufacturing. Thus, there is a huge demand for solutions which will promote early wound closure, mitigate contamination and provide better aesthetic results while also being cost-effective.

Porcine skin xenografts have been primarily investigated for burn wound dressing due to the physiological similarity between porcine and human skin, while also maintaining acceptable levels of healing efficiency and toxicity. Genetically modified alpha-1,3-galactosyl transferase knockout swine is used as a source of grafts as it does not provoke hypersensitive responses in recipients unlike wild porcine skin [19]. Unfortunately, porcine skin is also known as a carrier of various human pathogens and diseases, requiring extensive pathogenic inactivation procedures before it can be used, which removes almost all biological components which accelerate wound healing and closure.

Acellular fish skin CTPs, sourced from Atlantic cod or Nile Tilapia, carry no risk of transmission of pathogens due to it being sourced from a marine environment, which is vastly different from the one required by human pathogens to survive [3]. Thus, it requires little to no screening and can retain much of its valuable lipid profile, rich in Omega-3 PUFAs which accelerate wound healing and closure. A clinical study by Wallner et al. [20] tested Atlantic cod fish skin CTP against a synthetic skin substitute (Suprathel) and found out that the former performed better in terms of pliability, pigmentation, relief, pain, and itch, with improved aesthetic and functional outcomes compared to the latter (Figure 3) [20].

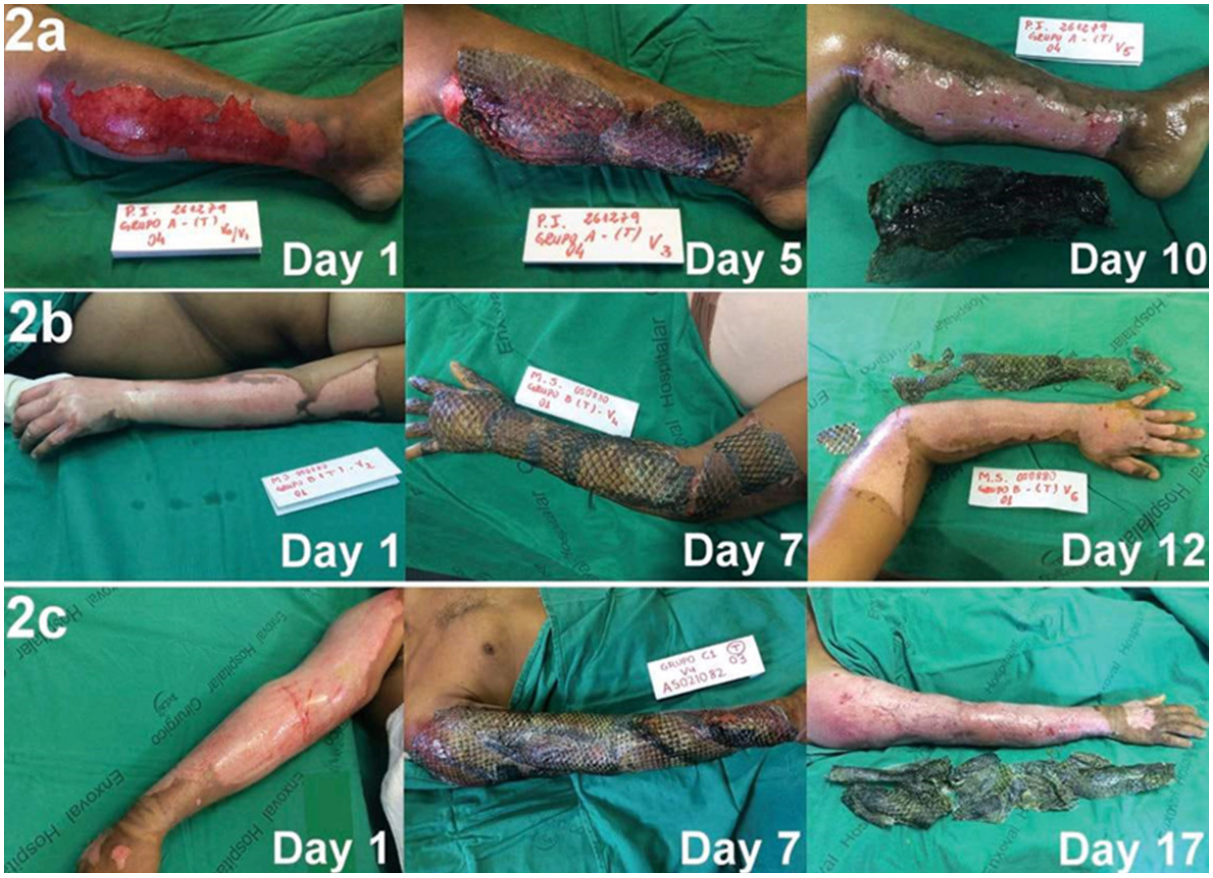

Figure 3: Application of fish skin CTPs to heal severe burn wounds on skin [4].

Treatment of diabetic foot ulcers

It is estimated that two thirds of patients with diabetes will develop peripheral neuropathy leading to loss of sensation, pain and abnormal foot architecture, a quarter will develop a foot ulcer. Therefore, diabetes associated foot complications place a considerable burden on healthcare resources and would likely get worse without advances in their treatment and management. Despite adherence to NICE (National Institute of Health and Care Excellence) guidelines which focuses on offloading and debridement, consideration of cardiovascular risk factors and tight glycemic control, healing rate of diabetic foot ulcers are poor. Chronic ulcers are at a high risk of eventual infection and seem to be a marker for amputation. Generally, such wound management strategies are divided into two main groups: Active management and passive management. Passive management involves the use of acellular dermal matrices as well as various types of dressings and offloading techniques. One such novel dressings which has been subjected to small clinical trials, known as Kerecis Omega3 which

is an intact fish skin rich in omega 3. The fish skin graft appears to convert the wound from an inflammatory to a healing stage, effectively promoting a normal healing process. The technology provides a natural structure that contains proteins and fats (including omega-3 fatty acids) allowing stem cells and cells to migrate in the fish skin graft where they create new dermal tissue to seal the wound [21].

Kerecis Omega3 was approved by the FDA (Food and Drug Administration) in 2013 for the management of various types of wounds and has been gradually extended worldwide. Due to the significant weakening of the body's glucose metabolism, the loss of wound healing potential is the main effect of diabetes. The high blood glucose concentration in the body also promotes the colonization and proliferation of bacteria in local tissues, induces biofilm to cover the wound, and deteriorates the wound environment. Advanced glycation end products can directly catalyze the excessive production of Reactive Oxygen Species (ROS), followed by the imbalance of M1 macrophages that are difficult to convert into M2 macrophages. ROS can also directly damage the blood vessels of the wound, making nutrients and oxygen difficult to transport to the wound [22]. The pathological process of diabetic wounds is the root cause of the development of wounds into chronic wounds.

The most superior feature of Acellular Fish Skin Grafts (ASFGs) is its lipid characteristics. The main components of many omega-3 polyunsaturated fatty acids are Docosahexaenoic Acid (DHA) and Eicosapentaenoic Acid (EPA). These two substances have antibacterial and anti-inflammatory properties and can even fight against methicillin-resistant Staphylococcus aureus [3,17]. Coraça-Huber, et al. (2021) tested the antibacterial toxicity of EPA and DHA to *S.epidermidis* in a study and found that high concentrations of unsaturated fatty acids have killing activity on planktonic cells and can cause inhibition of biofilms. At present, research on AFSG in the treatment of diabetic wounds has not explored its antibacterial role yet.

The skin of Atlantic cod is very similar to that of humans, which has three layers: epidermis, middle layer, and basal epithelium. Each layer of tissue has noteworthy porous structure and an average thickness of 450 microns. Because no chemicals and detergents are used in the decellularization process, the Atlantic cod skin retains good mechanical properties [1,3]. Compared with other wound dressings, AFSGs are more suitable for the treatment of diabetic wounds at different depths. Christy, et al. [2] proved that AFSGs can accelerate the closure of deep wounds, which can increase the early blood flow of wound healing. Ibrahim, et al. [16] compared the efficacy of AFSGs with other wound healing techniques in a study. They found that AFSGs had better wound healing than alginate collagen dressings, 1% silver sulfadiazine cream, and other xenotransplantations [16].

The main content of cod skin matrix is type I collagen, which not only has good thermal stability and can better adapt to the wound environment, but also has the effect of efficient combination with proinflammatory cytokines. Lullovede, et al. [23] compared the therapeutic effects of standard care (collagen dressing) and AFSGs transplantation with the percentage of wound healing in the twelfth week as the end point of treatment. At the sixth week, the AFSGs transplantation group reduced the wound area by 72.8%, which was significantly better than the standard nursing effect (32%) [23]. Therefore, we can see that the AFSGs is also extraordinarily effective in wound care therapy. The AFSGs has a good effect in both active treatment and passive treatment. It breaks the barrier of traditional treatment methods and plays a remarkable transitional role in both aspects.

AFSGs for treatment of combat wounds

Improvised explosive devices and new directed energy weapons are changing warfare injuries from penetrating wounds to large surface area thermal and blast injuries. Acellular fish skin is used for tissue repair and during manufacturing subjected to gentle processing compared to biologic materials derived from mammals. This is due to the absence of viral and prion disease transmission risk, preserving natural structure and composition of the fish skin graft. Cadaver skin is the preferred burn wound cover for severe burns and is frequently used in the hospital setting. The use of cadaver skin is, however, impractical in battlefield and other austere environments [24]. To respond to this unmet clinical need, attempts have been made to develop several types of skin substitute in recent years. The main types of skin substitutes are either cellular or acellular. Cellular skin substitutes are not practical for use in a combat theater, as they either need special stabilization fluids with short shelf life or be frozen in liquid nitrogen [24]. Acellular mammalian-derived products possess prolonged shelf life as compared to cellular skin substitutes but per FDA requirements must undergo "viral inactivation." Viral inactivation is performed with detergents that remove all soluble components from the tissue leaving behind an inert matrix of collagenous structure. The harsh viral inactivation processing removes lipids, glycans, elastins, hyaluronic acid, soluble collagen, and other important biological components from the tissue that potentially are beneficial to wound healing [25].

Double-blind randomized clinical trials have shown that wound treatment with acellular fish skin allows for significantly faster wound closure than porcine small-intestinal-derived matrices [26]. After grafting, the fish skin is incorporated into the damaged area and infiltrated by autologous cells that convert the graft into functional, living tissue while the graft slowly breaks down. The fish skin graft has been used to treat a large number of wounds of various etiologies, both acute and chronic. he acellular fish skin is currently being used in a regulatory approved and patented wound treatment product being marketed in the United States and in Europe under the brand name Kerecis Omega3 [1].

Discussion

Overall, fish scale skin grafting shows promise as a potential alternative to traditional skin grafting techniques. Skin grafting from fish scales, also known as piscine xenografting, is a novel approach to treating severe burns and skin injuries. The comprehensive review on accelerated regeneration of human skin using acellular fish skin grafts highlights the remarkable potential of this innovative

approach in revolutionizing wound care and tissue regeneration. By harnessing nature's biomimicry and leveraging the unique structural, biochemical, and immunomodulatory properties of fish skin, acellular grafts offer a promising solution for addressing the limitations of traditional wound management strategies. Through a synthesis of evidence from experimental studies, clinical trials, and mechanistic investigations, the review elucidates the diverse applications of acellular fish skin grafts in promoting accelerated wound healing, reducing scar formation, and enhancing tissue regeneration across a spectrum of acute and chronic wound conditions. Furthermore, the review underscores the importance of ongoing research efforts in optimizing graft design, manufacturing processes, and clinical delivery methods to maximize therapeutic efficacy and ensure widespread accessibility of fish skin-derived products. Overall, acellular fish skin grafts represent a paradigm shift in the field of regenerative medicine, offering new avenues for improving patient outcomes and restoring skin integrity in the pursuit of enhanced quality of life. The included research focused on the total re-epithelialization time of burn wounds treated with AFS and the potential reduction in pain, appropriate dressing changes, and medical costs. However, there is a need for larger randomized and controlled trials of this therapy for different types of chronic wounds to establish the role of decellularized fish skin grafts as a viable clinical option [27].

Conclusion

Piscine xenograft is a novel approach to wound healing and human skin regeneration, notable for its unique properties, such as an astonishing similarity to human skin, its ability to promote cellular migration and its innate immunomodulatory properties. Furthermore, this material is anti-inflammatory, antimicrobial, antiviral, hypoallergenic and has analgesic effects. This is thought to be largely due to the retention of naturally derived compounds within the collagen scaffold, including an extremely high content of omega-3 fatty acids like EPA and DHA. Several studies have shown the effectiveness of fish skin CTPs in the treatment of both surface level and deep level wounds from various sources, such as burns, diabetic foot ulcers and battlefield injuries. Furthermore, the comparatively simple nature of its manufacturing process and low cost, coupled with a long shelf life and ease of storage at room temperatures, makes it a highly valuable form of treatment in remote and adverse environmental conditions, as well as in economically underdeveloped countries. However, a greater number of randomized and controlled trials with well-established control groups need to be performed to demonstrate better efficacy of this treatment. Moreover, further research must be performed to explore the potential role of piscine CTPs beyond near surface-level wounds, such as in tendon regeneration procedures.

References

1. Magnússon S, Baldursson BT, Kjartansson H, Rolfsson Ó, Sigurjónsson GF (2017) Regenerative and antibacterial properties of acellular fish skin grafts and human Amnion/Chorion membrane: Implications for tissue preservation in combat casualty care. Military Medicine 182(S1): 383-388.
2. Stone R, Saathoff EC, Larson DA, Wall JT, Wienandt N, et al. (2021) Accelerated wound closure of deep partial thickness burns with acellular fish skin graft. International Journal of Molecular Sciences 22(4): 1590.
3. Fiakos G, Kuang Z, Lo E (2020) Improved skin regeneration with acellular fish skin grafts. Engineered Regeneration 1: 95-101.
4. Júnior EML, Moraes FD, Costa MO, Rohleder BA, Rocha AVP, et al. (2020) Innovative burn treatment using Tilapia skin as a xenograft: A Phase II randomized controlled trial. Journal of Burn Care & Research 41(3): 585-592.
5. Lin X, Kong B, Zhu Y, Zhao Y (2022) Bioactive fish scale scaffolds with MSCs-loading for skin flap regeneration. Advanced Science 9(21): e2201226.
6. Seth N, Chopra D, Lev-Tov H (2022) Fish skin grafts with omega-3 for treatment of chronic wounds: Exploring the role of Omega-3 fatty acids in wound healing and a review of clinical healing outcomes. Surg Technol Int 40: 38-46.
7. Rotman S, Koch N, Wiesner L, Aubert V, Rosales IA, et al. (2019) Nonvascularized human skin chronic allograft rejection. American Journal of Transplantation 19(11): 3191-3196.
8. Alam K, Jeffery SLA (2019) Acellular fish skin grafts for management of split thickness donor sites and partial thickness burns: A case series. Military Medicine 184(Suppl 1): 16-20.
9. Li D, Sun WQ, Wang T, Gao Y, Wu J, et al. (2021) Evaluation of a novel tilapia-skin acellular dermis matrix rationally processed for enhanced wound healing. Materials Science & Engineering C Materials for Biological Applications 127: 112202.
10. Bružauskaitė I, Bironaitė D, Bagdonas E, Bernotienė E (2016) Scaffolds and cells for tissue regeneration: Different scaffold pore sizes-different cell effects. Cytotechnology 68(3): 355-369.
11. Sitje TS, Grøndahl EC, Sørensen JA (2018) Clinical innovation: Fish-derived wound product for cutaneous wounds. Wounds International 9(4): 44-50.
12. Magnusson S, Winters DPMC, Baldursson BT, Kjartansson H, Rolfsson O, et al. (2016) Acceleration of wound healing through utilization of fish skin containing omega-3 fatty acids. Wound Care 5: 10.
13. Nobre MEP, Correia AO, Borges DB, Sampaio M, Chakraborty TMA, et al. (2013) Eicosapentaenoic acid and docosahexaenoic acid exert anti-inflammatory and antinociceptive effects in rodents at low doses. Nutrition Research 33(5): 422-433.
14. Jeschke MG, Baar MEV, Choudhry MA, Chung KK, Gibran NS, et al. (2020) Burn injury. Nature Reviews Disease Primers 6(1): 11.
15. Saavedra PE, Leal OJVD, Areda CA, Galato D (2021) The costs of burn victim hospital care around the world: A systematic review. Iranian Journal of Public Health 50(5): 866-878.
16. Ibrahim MIM, Ayyoubi HS, Alkhairi LA, Tabbaa H, Elkins I, et al. (2023) Fish skin grafts versus alternative wound dressings in Wound care: A systematic review of the literature. Curēus 15(3): e36348.
17. Luze H, Nischwitz SP, Smolle C, Zrim R, Kamolz L (2022) The use of acellular fish skin grafts in burn wound management—A systematic review. Medicina (Kaunas) 58(7): 912.
18. Mahdavi-Mazdeh M, Heshmati BN, Tavakoli S, Ayaz M, Ardalan FA, et al. (2013) Human split-thickness skin allograft: skin substitute in the treatment of burn. Int J Organ Transplant Med 4(3): 96-101.
19. Leonard DA, Mallard C, Albritton A, Torabi R, Mastroianni M, et al. (2017) Skin grafts from genetically modified α-1,3-galactosyltransferase knockout miniature swine: A functional equivalent to allografts. Burns 43(8): 1717-1724.
20. Wallner C, Holtermann J, Drysch M, Schmidt S, Reinkemeier F, et al. (2022) The use of intact fish skin as a novel treatment method for deep

dermal burns following enzymatic debridement: A retrospective case-control study. European Burn Journal 3(1): 43-55.

21. Woodrow T, Chant T, Chant H (2019) Treatment of diabetic foot wounds with acellular fish skin graft rich in omega-3: A prospective evaluation. Journal of Wound Care 28(2): 76-80.

22. Powers JG, Higham C, Broussard K, Phillips TJ (2016) Wound healing and treating wounds. Journal of the American Academy of Dermatology 74(4): 607-625.

23. Lullove EJ, Liden B, Winters C, McEneaney P, Raphael A, et al. (2021) A multicenter, blinded, randomized controlled clinical trial evaluating the effect of Omega-3–Rich fish skin in the treatment of chronic, nonresponsive diabetic foot ulcers. Wounds 33(7): 169-177.

24. Calota D, Nitescu C, Florescu I, Lascar I (2012) Surgical management of extensive burns treatment using allografts. J Med Life 5(4): 486-490.

25. Crapo PM, Gilbert TW, Badylak SF (2011) An overview of tissue and whole organ decellularization processes. Biomaterials 32(12): 3233-3243.

26. Baldursson BT, Kjartansson H, Konrádsdóttir F, Gudnason P, Sigurjonsson GF, et al. (2015) Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa: A noninferiority study. The International Journal of Lower Extremity Wounds 4(1): 37-43.

27. Zhao C, Feng M, Gluchman M, Ma X, Li J, et al. (2024) Acellular fish skin grafts in the treatment of diabetic wounds: Advantages and clinical translation. Journal of Diabetes 16(5): e13554.