Dermatology Practical & Conceptual

Omega-3 Acellular Fish Skin Grafts for Chronic and Complicated Wounds: A Systematic Review of Efficacy and Safety

Sonali Karhana[1], Mohd. Ashif Khan[1]

1 Department of Translational & Clinical Research, School of Chemical and Life Sciences, Jamia Hamdard, New Delhi, India

Key words: Acellular fish skin graft, Biopsy wounds, Diabetic foot ulcer, Wound healing, Wound therapy

Citation: Karhana S, Khan MA. Omega-3 Acellular Fish Skin Grafts for Chronic and Complicated Wounds: A Systematic Review of Efficacy and Safety. *Dermatol Pract Concept.* 2025;15(2):4945. DOI: https://DOI.org/10.5826/dpc.1502a4945

Accepted: November 26, 2024; **Published:** April 2025

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Dr. Mohd Ashif Khan, Department of Translational & Clinical Research, School of Chemical and Life Sciences Jamia Hamdard, Hamdard Nagar, New Delhi 110062, India. ORCID ID:0000-0003-1576-8779. Email: mhdashifkhan@gmail.com, makhan@jamiahamdard.ac.in

ABSTRACT

Introduction: A systematic review was conducted to investigate the efficacy of acellular fish skin grafts (AFSGs) for the treatment of complicated wounds. AFSGs can be used as a regenerative and antimicrobial tool for healing complicated wounds, but clinical evidence remains unclear.

Objective: This systematic review aimed to summarize the efficacy of AFSGs on complicated wounds using evidence from existing published studies.

Methods: Electronic databases like PubMed, ScienceDirect, Google Scholar, and Clinicaltrials.gov were searched for relevant literature reporting on the efficacy of AFSGs for wound healing. Based on the inclusion and exclusion criteria, nine studies were selected for data extraction. The quality of the articles was evaluated using the RoB 2 and ROBINS-I tools.

Results: Existing evidence shows that AFSGs accelerate wound healing, reduce pain, prevent antibiotic administration, and cause no autoimmune reactions. The total re-epithelialization time for diabetic foot ulcers (DFUs) was observed as 15 ± 8 weeks, depending on the severity of the ulcers. Acute full thickness biopsy wounds healed within 3.75 ± 0.25 weeks. As reported in papers, AFSGs showed significantly better effects than standard-of-care therapy, collagen alginate dressings, dehydrated human AMNION/chorion membrane, and/ or porcine small-intestine submucosa. However, instances of rashes, erythema, pain, and hypergranulation were reported when AFSGs were applied to biopsy wounds.

Conclusion: Overall, the evidence obtained in this systematic review indicates that AFSGs represent a clinically and financially effective option for the treatment of wounds when compared with conventional alternatives.

Introduction

Wounds are identified as a break or separation from the continuity of skin or tissue caused by physical, biological or chemical factors [1]. The economic, social, and clinical impact of wounds is on the rise, and novel strategies for wound management and treatment are needed. The global wound care market is growing at a compound annual growth rate (CAGR) of 6.6% (period 2020–2027) and is estimated to reach USD 18.7 billion by 2027 [2]. The hard-to-heal wounds frequently encountered in wound care practice include diabetic foot ulcers (DFUs), venous leg ulcers (VLUs), post-surgical wounds, and wound dehiscence. DFU is a chronic wound, with its market expected to reach USD 11.05 billion by 2027 [3]. Despite recent developments, the incidence of DFUs has not decreased in the last two decades [3]. DFU is the leading cause of hospitalization among diabetic patients, accounting for 25% of hospital admissions [4]. Moreover, 14%-24% of foot ulcer patients have to undergo amputations [5]. In addition, the global market of venous ulcers is estimated to reach USD 4.8 billion, growing at a CAGR of 6.4% (2019-2026) [6]. Another problem that has remained to be dealt with in the last several decades is that of wound dehiscence. Post-laparotomy wound dehiscence occurs in approximately 0.25% to 3% of patients who undergo the procedure, necessitating immediate surgical intervention, with a mortality rate of 20% [7]. Additionally, traumatic wounds, surgical wounds, and superficial burns or abrasions are classified as acute wounds. Acute biopsy wounds are also prevalent among patients, in which case inadequate treatment of such acute wounds leads to the formation of chronic wounds [8]. Apart from the financial impact, hard-to-heal wounds impose a significant degradation in patients' quality of life. Several treatment strategies have been introduced that promote wound healing by accelerating the healing process at a molecular level [9-11]. Existing topical agents include iodine solutions, hypochlorous acid, cadexomer iodine, and collagenase [12,13]. Similarly, several types of dressings are now available, like acrylics, honey alginates, alginates, micronized collagen, hydrocolloids, hydrofibers, and oxidized regenerated cellulose [14]. These products are also available with silver for its anti-microbial effects [15-17]. However, while these dressings and topical therapies are effective, chronic wounds cannot be cured without proper debridement, offloading, and management of infection [18]. Advanced therapies like negative pressure wound therapy and hyperbaric oxygen therapy have proven effective, but they require repeated hospital appointments, thus reducing patient compliance. Other advanced therapies include stem cell (autogenous and allogeneic), amniotic tissue, and umbilical cord-based therapies, for which prospective data have yet to show their efficacy in facilitating wound healing and are quite expensive for the patients [19,20]. With the rise in hard-to-heal chronic and complex acute wounds, developing new strategies that facilitate effective treatment is essential. One of the recent novel strategies coming up on the market is the use of the acellular dermal matrix (ADM). ADM is a type of surgical mesh developed from animal or human skin in which the cells are separated from the support structure [21]. ADM stimulates angiogenesis and provides a scaffold for the formation of granulation tissue. Formerly regarded as merely passive collagen structures that offer a framework for cellular growth, ADMs are now recognized for their active role in tissue regeneration while interacting with growth factors involved in the wound healing process [22,23]. Among the many clinically available acellular dermal matrices, the acellular fish skin graft (AFSGs) product Kerecis (Coloplast; Humlebaek, Denmark) is gaining popularity among hard-to-heal wounds [24]. It is an omega-3 fatty acid-rich fish skin product derived from north Atlantic cod (*Gadus morhua*) found in Ísafjörður, Iceland. It is homologous to any human skin, and it retains its natural omega-3 polyunsaturated fatty acids [25]. In addition, there is no documented risk of viral disease transmission from cold-water fish to humans [26]. The key efficacy of AFSGs lies in their lipid profile. They are abundant in omega-3 polyunsaturated fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), known for their anti-inflammatory and antimicrobial characteristics [27,28]. Thus, AFSGs obtained from Atlantic cod offer an interesting option for treating complicated wounds. By complicated wounds, we mean wounds that show delayed healing due to factors such as poor vascularization, chronic inflammation, infection, and high recurrence rates, commonly observed in diabetic foot ulcers, venous ulcers, and full-thickness biopsy wounds. Although acute biopsy wounds may generally heal faster than chronic ulcers, full-thickness biopsy wounds can still present complications. Due to complexities in their healing mechanisms, these wounds often require advanced wound care approaches beyond standard-of-care treatments. This systematic review grouped all the existing study cohorts together to investigate the efficacy of fish skin grafting in healing complicated wounds.

Objectives

This systematic review aimed to summarize the efficacy of AFSGs on complicated wounds using evidence from existing published studies. It was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 guidelines (Figure 1 and Table S1). The review is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration ID - 382204.

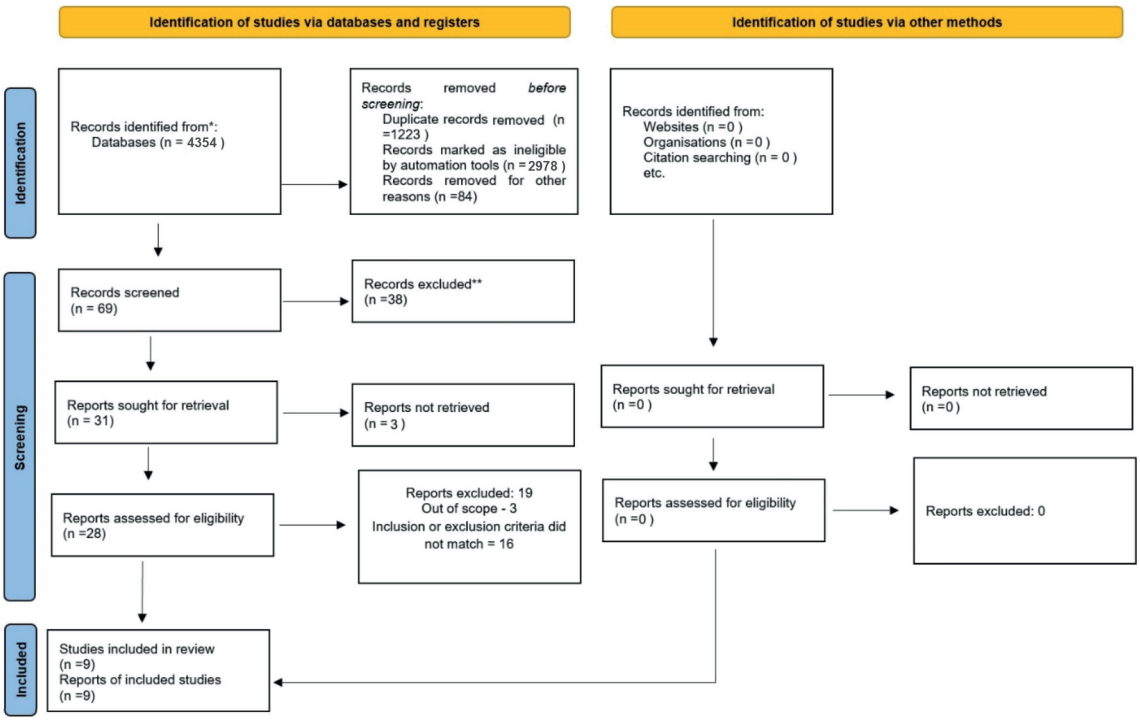

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) 2020 - flow diagram of the inclusion and exclusion criteria. *Pubmed, ScienceDirect, Google Scholar, Cochrane.

Methods

Data Sources

We performed a systematic search of the medical literature using the electronic databases ScienceDirect, PubMed, Cochrane, and Google Scholar. The search for unpublished studies was done on Clinicaltrials.gov. The following terms were variously combined in the search strategy: "acellular fish skin", "fish skin grafts", "fish skin", "wound healing", "diabetic foot ulcer", "venous foot ulcer", "acute biopsy wounds". In addition to this, the reference lists of the included reports were screened manually in order to get relevant publications.

Selection Criteria

Selection of the relevant articles was performed by employing the Rayyan online tool; both title-specific and abstract-specific searches were carried out using the tool. The independently nominated articles were matched, and a consensus was reached after multiple discussions among the authors. The selected reports were then subjected to full-text investigations per the inclusion and exclusion criteria. Complicated wounds were defined as "hard-to-heal" wounds that show delayed healing due to factors like chronic inflammation, limited vascularity, infection, deep cuts involving subcutaneous tissue, and high recurrence rates [29]. Original articles in English reporting the efficacy of fish skin grafts for wound healing were considered as the essential inclusion criterion. Exclusion criteria included a) review articles, b) case series with fewer than five enrolled patients, and c) book chapters.

Data Extraction

The studies eligible according to the inclusion criteria were assessed for outcome measures like total re-epithelialization time, additional interventions, adverse events, and follow-up for a dressing change. The data were extracted from the full-text articles onto an Excel spreadsheet. All the discrepancies were rectified by the authors, and the data were approved by the principal investigator.

Quality Assessment

The selected publications were assessed for quality by employing the RoB 2 tool for randomized studies and the ROBINS-I tool for non-randomized studies/case series (Figure 2). The RoB 2 tool for randomized trials (RCTs) covers six domains for bias assessment ranging from the randomization process to the selection of reported result. ROBINS-I tool for non-randomized trials, on the other hand, includes seven domains to assess the quality of the studies. The authors independently evaluated the data before reaching a consensus on risk-of-bias judgments (Tables S2 and S3).

Results

A total of nine studies reporting the efficacy of AFSGs in patients with complicated wounds, including DFUs, venous

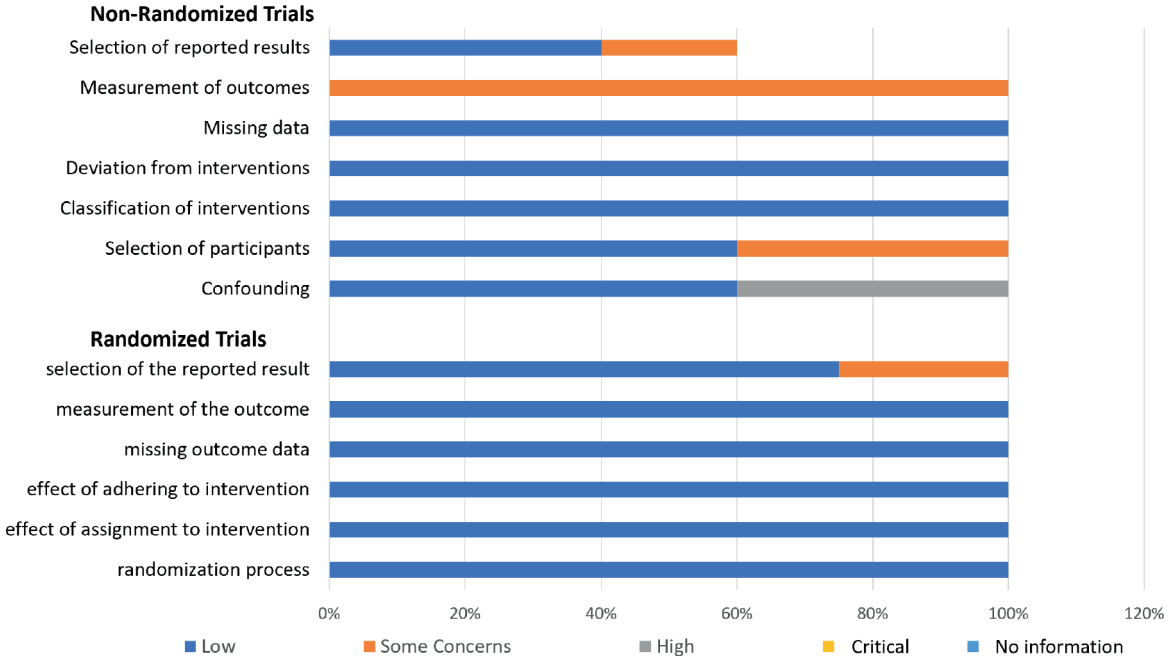

Figure 2. Risk of bias judgement of the included non-randomized and randomized studies using Cochrane's ROBINS-I and RoB 2 tools, respectively.

foot ulcers, acute biopsy wounds, et cetera, were included in this systematic review. All the included studies were in English. The primary outcome assessed was the re-epithelialization time by the application of AFSGs. Tables 1 and 2 summarize the baseline characteristics and study outcomes of the studies included in the systematic review.

Total Re-epithelialization Time

The primary focus of all the studies included in this systematic review was the total re-epithelialization time of the treated wounds. Based on the studies analyzed that reported the healing duration of DFUs, the total re-epithelialization time ranged from seven to 23 weeks, with a mean duration of 15 ± 8 weeks and a median value of 12.42 weeks. This is in contrast with the median healing time of six months in 1999/2000 and 6.6 months in 2011/2012 with standard of care (SoC) procedures [30]. A recent study reported that 50.9% of diabetic feet do not heal by the end of 12 weeks, with 1.3% of deaths [31]. Thus, AFSG shows significant improvement over SoC treatment. Woodrow et al. conducted a prospective study on nine patients with DFU in the United Kingdom and reported a mean re-epithelialization time of 20.42 weeks. Lullove et al. conducted two RCTs in consecutive years with 94 and 49 chronic DFU patients (Texas grade 1A/1C), reporting a mean of seven and 12 weeks, respectively. Both the studies compared AFSG with collagen alginate dressings and noted a statistically significant difference in patient outcomes. The team reported that by the end of six weeks, there was a 41.2% reduction in the percentage area of wound in the collagen alginate group, while the fish skin group exhibited a reduction of 72.8%. Similar results were reported by Zehnder et al.[32] (25), who reported that chronic DFUs were completely healed in 12.42 weeks. Dorweiler et al. [33] also included chronic DFU patients who were additionally administered with antibiotic therapy, analgesics, and opioids. They reported a re-epithelialization time of about 23 weeks, with a significant reduction in analgesics. The difference in mean re-epithelialization time between the studies by Lullove et al. and Dorweiler et al. can be attributed to the wound types. Lullove et al. studied mild ulcers (Texas grade 1A/1C), while Dorweiler et al. included patients with more severe lower limb ulcers involving amputation and exposed bone, which are harder to heal. Notably, Dorweiler et al. mentioned that adequate debridement, bacterial control, and tissue perfusion are the prerequisites for fish skin application to the wounded site to attain minimum re-epithelialization time.

In the case of biopsy wounds, the total healing time was reported in the range of 3.5 to 4 weeks, with a mean and median value of 3.75 weeks. In contrast, without any treatment, it took six weeks to achieve just 50% of the wound's tensile strength [34]. Kirsner et al. concluded that in comparison to biopsy wounds treated with dehydrated human amnion-chorion membrane (dHACM), wounds treated with fish skin showed a notably faster healing rate (hazard ratio F2.37; 95% CI: 1.75–3.22; *P*=0.0014). The study also reported that wounds treated with dHACM were, on average, 76% more expensive to treat than those treated with acellular fish

Table 1. Baseline Characteristics of Patients in Reports Evaluating the Application of Acellular Fish Skin Grafts for Wound Healing.

Study No	Author	Study Design	Wound Type	Patients Analyzed (C/T)	Age (Years)	Race/Countries	Wound Size	Wound Classification	Comparator
1	Woodrow et al. 2019	Prospective observational study	Diabetic foot ulcer	9	65 (54 - 88)	United Kingdom	0.94 cm^2 to 29.55c m^2	Acute (6); chronic (3) Texas grade 1 to 3[2]	None
2	Lullove et al. 2022	Prospective RCT	Diabetic foot ulcer	94 (48/46)	58 (48.5-64)	USA	1 cm^2 to 25 cm^2	Chronic; Texas grade 1A/1C	Collagen alginate dressing (fibracol plus collagen wound dressing with alginate; 3M)
3	Lullove et al. 2021	Prospective RCT	Diabetic foot ulcer	49 (24/25)	64.95	USA	1 cm^2 to 25 cm^2	Chronic; Texas grade 1A/1C	Collagen alginate dressing
4	Zehnder et al. 2022	Outcome-based model study	Venous leg ulcers and diabetic foot ulcers	42 (21/21)	NR*	Switzerland	1.4 cm^2 (0.12 cm^2 to 36.2 cm^2)	Chronic	4 weeks of Standard-of-care (SOC*) therapy
5	Dorweiler et al. 2018	Prospective observational study	Diabetic foot ulcer (Amputation patients included)	8	50 - 101	Germany	23 ± 18 cm^2 (range 6–63cm^2)	Chronic	None
6	Kirsner et al. 2020	Double-blind prospective RCT	Full-thickness biopsy wounds	85	24.1 (19-51)	Iceland (84 Caucasians and 1 of African origin)	0.12 cm^2	Acute	dHACM (dehydrated human AMNION/chorion membrane)
7	Baldursson et al. 2015	Double-blind prospective RCT	Whole thickness biopsy wounds	81 (40/41)	NR	African, Hispanic, Caucasian	0.12 cm^2	Acute	Porcine Small-Intestine Submucosa
8	Guido Ciprandi et al. 2024	Case series	Animal bite, sacral pressure ulcer, machinery accident, surgical dehiscence	15	8 years 9 months	Italy	5.8 cm^2	Chronic	None
9	Ibrahim Cherry et al. 2023	Case series	3rd degree burn, chronic wound on scalp, scar revision, hidradenitis suppurative	5	1,2, 9,14, 16	Switzerland	53 cm^2	Chronic, scarring	None

Abbreviations: C/T = Control/Treatment; RCT = randomized controlled trial; SOC = standard of care (offloading, appropriate debridement, and moist wound care).

Table 2. Clinical Studies Reporting the Application of Acellular Fish Skin Graft for Complicated Wounds.

Study No.	Author	Dressing Procedure and Time Period	Additional Intervention	Adverse Events	Wound Observation Technique	Total Re-epithelialization Time	Conclusion
1	Woodrow et al. 2019	Dressings were changed weekly for 6 weeks	None	No skin irritation, no increased pain. Amputation - 1	Digital photography and ImageJ software	20.42 weeks	Fish skin grafts accelerate wound healing.
2	Lullove et al. 2022	Dressings were changed weekly for 6 weeks and 12 weeks, respectively	None	NR	Site investigator's assessment. Reviewed by a vascular surgeon, a podiatrist, and an internal medicine specialist.	7 weeks	Statistically significant difference in healing was observed between patients treated with AFSGs and those treated with collagen alginate dressings.
3	Lullove et al. 2021	Dressings were changed weekly for 12 weeks	None. Debridement was done before initiation.	NR	Site investigator's assessment	12 weeks	Fish skin grafting can be employed for patients with chronic DFU in combination with SOC therapy.
4	Zehnder et al. 2022	Dressings were changed weekly. 8 weeks	None	NR	Digital Photography	12.42 weeks	Fish skin grafts show faster healing rates than SOC therapy.
5	Dorweiler et al. 2018	Dressings were changed weekly until complete wound healing	Antibiotic therapy, analgesics and opioids	No infections or immune reactions occurred during the treatment period. Significant pain reduction.	Digital Photography	23 ± 10 weeks	Reduction in analgesics uptake. Fish skin graft is effective in treating complicated wounds
6	Kirsner et al. 2020	Dressings were changed weekly for 6 weeks	None	Rashes-6 Erythema - 6 Pain - 7 Skin irritation with discharge - 2 Hypergranulation - 2	Digital Photography	3.5 weeks	Fish skin graft treated wounds healed significantly faster (hazard ratio 2.37) when compared to dHACM-treated wounds.

7	Baldursson et al. 2015	On each return visit, if the treatment material was completely intact, it was left in the wound. If not, new material was applied to the wound; 4 weeks	None	Erythema - 1 Skin irritation and discharge - 2 No infection was reported. No immune reactions recorded.	Digital photography	4 weeks	Fish skin graft healed the wounds significantly faster than Porcine Small-Intestine Submucosa
8	Guido Ciprandi et al. 2024	As per requirement (2-3 dress changes were required); 54 weeks	Negative pressure wound therapy to 12/15 patients	None	Digital photography	12.4 days	No residual scarring was observed after 12 months. The operating time was reduced to <60 min. Accelerated wound healing with full granulation tissue coverage was observed in 100% of the patients.
9	Ibrahim Cherry et al. 2023	NR	Physiotherapy for scar massage	No hypersensitivity or allergic reaction was reported.	Digital photography	48.6 days	Fish skin graft presents skin elasticity, has analgesic potential due to Omega-3 fatty acids, and stimulate myofibroblast activity. Fish skin can be applied to diverse wound types and anatomical sites.

Abbreviations: AFSG = acellular fish skin graft; NR = not reported; SOC = standard of care offloading, appropriate debridement, and moist wound care).

skin. Baldursson et al. employed the noninferiority test to assess the effectiveness of fish skin ADM in comparison to porcine small-intestine submucosa extracellular matrix for the healing of 162 full-thickness biopsy wounds (4 mm) on the forearms of 81 volunteers. They reported that AFSG was noninferior and healed at an average of 28 days.

Dressing Changes

Different teams of researchers adopted different procedures for dressing the fish skin graft as it mainly depended upon the type of wound being treated. All the studies reporting the application of AFSGs on DFUs adopted a weekly change of dressings [32], [33], [35], [36]. The same procedure was adopted by Kirsner et al. for acute biopsy wounds. On average, each subject received approximately 1.6 applications of the AFSG, whereas the dHACM group received approximately 1.4 applications per wound, showing no significant difference between the two groups [37]. Studies on acute biopsy wounds by Baldursson et al. also employed AFSGs but changed the dressing only if the fish skin graft was not completely intact [38], [39].

Adverse Events

Woodrow et al. reported no case of skin irritation and increased pain when treating DFUs with AFSG, but the team also reported a single case of amputation in spite of the patient's undergoing treatment with AFSGs [35]. No adverse event was reported by Lullove et al. and by Zehnder et al in DFU and venous foot ulcer patients undergoing fish skin grafting [32], [36]. On similar grounds, Dorweiler et al. stated that no immune reactions or infections were observed when employing AFSG during the whole treatment period for DFUs. Moreover, the matrix provided antinociceptive and anti-inflammatory effects [33]. For acute biopsy wounds, Kirsner et al. reported the development of rashes, erythema, pain, hyper granulation, and skin irritation with discharge on the application of AFSG [37]. Similarly, erythema and skin irritation with discharge was reported by Baldursson et al. when fish skin graft was used for biopsy wounds. Additionally, the team recorded no infection or immune reaction [38].

Conclusions

There exists evidence demonstrating the potential application of acellular dermal matrix of marine origin for wound healing in human subjects [40] as well as in pre-clinical models [41-43]. A recent study on rat and mini-pig skin wound models reported that AFSGs significantly accelerated wound healing through granulation growth, angiogenesis, and collagen deposition. The team also noted a high expression of alpha-smooth muscle actin (α-SMA), transforming growth factor-beta 1 (TGF-β1), and CD31, all of which are actively involved in the wound healing process [44]. Another study on a rat wound model found that AFSGs stimulate factors crucial to repairing skin, blood vessels, and nerves, including fibroblast growth factor (FGF) and epidermal growth factor (EGF), while preventing external infections [45].

As a part of the clinical evidence, a case study on a patient suffering from hemophilia and chronically infected ulcerations on a dehisced transmetatarsal amputated left foot showed that by using six applications of AFSGs, the ulcerations healed in 14 weeks [46]. Another case study on split-thickness donor sites showed that on the application of fish skin graft, the wounds healed on average in 11.5 days, with zero incidence of any kind of adverse event [47]. A recent case study in the USA applied AFSG to a 61-year-old immunodeficient patient with a complex right flank wound, stool contamination, necrotizing soft tissue infection from perforated colon cancer, and sepsis. AFSG healed the wound by exhibiting angiogenic and anti-inflammatory activity [48]. Another recent case study on two patients aged 62 and 42 years with chronic intra-abdominal catastrophe post-damage control laparotomy reported that the use of AFSG sped up the skin graft placement for both patients, reduced the need for wound vacuum-assisted closure (VAC), and consequently shortened their hospital stay [49].

The present study demonstrates that AFSGs show both regenerative and antimicrobial effects for healing complicated wounds. AFSGs consist of proteoglycans, glycosaminoglycans, fibrin, and collagen, which act as a substitute for human skin [50]. AFSGs regulate matrix metalloproteinase (MMP) activity by providing a breakdown site for the scaffold instead of the host tissue and extracellular matrix (ECM) components. This regulation prevents excessive pro-inflammatory cytokines, aiding wound healing and maintaining cellular processes [51]. AFSGs have higher levels of omega-3 fatty acids (DHA and EPA) than do mammalian grafts, making up 10.7% and 8.5%, respectively, of the lipid content. Omega-3 fatty acids accelerate wound healing, as shown in a study where healthy patients taking EPA (1.6 g) and DHA (1.2 g) healed blisters faster by day 5 compared to a control group on mineral oil and low-dose aspirin [52]. Additionally, AFSGs are also known to show anti-microbial effects, as depicted by Baldursson et al. [38] A recent study using a two-chamber assay on *Staphylococcus aureus* cultures found that fish skin acted as a bacterial barrier. The barrier function of fish skin improved by 80% when spiked with over 10% omega-3 fatty acids [53]. Also, researchers have stated that colony-forming units found in fish skin consist of non-infectious microbiota [54]. AFSGs have taken over mammalian skin grafts as fish skin does not transmit any disease, like variant Creutzfeldt-Jakob disease or bovine spongiform encephalopathy [55]. Therefore, there is no need

for a robust sterilization process for AFSGs [56]. Additionally, Baldursson et al. reported that fish skin-derived ADM treats full-thickness wounds without changing autoantibodies, indicating no autoimmune response in humans. [38].

AFSG rich in omega-3 fatty acid is easily available worldwide as a vacuum-dried product. The processing of the product is gentle, which enables it to retain its molecular composition and omega-3 polyunsaturated fatty acids (PUFA). Moreover, keeping sustainability in mind, Atlantic cod are not farmed and are always line-caught, which is highly regulated by the government of Iceland. Present indications, as stated by the company's official website, include partial and full-thickness wounds, trauma wounds, burns, soft tissue reinforcement, surgical wounds, DFUs, venous ulcers, pressure ulcers, and draining wounds [49]. However, in spite of including full-thickness wounds as a part of the applicability of AFSGs, mild adverse events such as rashes, erythema, hyper granulation and skin irritation with discharge were observed by Kirsner et al. and by Baldursson et al. [37-38]. Thus, extra precautions should be taken when treating acute biopsy wounds with AFSGs.

The present study highlights the potential of AFSGs as a regenerative and antimicrobial solution for complex wound healing. It should also be noted that adequate debridement and SoC should not be overlooked when employing AFSGs for good patient outcomes. All the studies included in this systematic review, in conjunction with a recent cost analysis published by Winters et al.[57] based on a Monte Carlo simulation [57] reporting that fish skin grafting is 93.6% more likely to be a cost-effective choice, demonstrate the value and suitability of the procedure in the years to come.

The relevance of existing reports on the efficacy of AFSGs for wound healing is limited, as this therapeutic strategy is relatively new. As a result, there are fewer studies available on the applicability of fish skin in wound healing. Trials should be designed by widening the scope of wounds included in the studies, e.g., venous foot ulcers and many such chronic conditions. Moreover, a meta-analysis could not be conducted due to the heterogeneity of study designs and outcome measures across the included studies. Additionally, the lack of a homogeneous control group across studies limited the ability to directly compare the outcomes. Thus, future studies with standardized methodologies and control groups are needed to validate the effectiveness of AFSG for complicated wound management.The available literature suggests that AFSGs are effective for treating complex wounds. AFSGs are able to heal the whole wound area at a faster rate, demonstrate anti-inflammatory and antinociceptive effects, cause less pain, and decrease the number of follow-ups for of dressing changes. One of the major findings of this systematic review is that antibiotics need not be administered in association with fish skin grafting. Therefore, AFSGs can not only be employed for their regenerative effects but also for their antiseptic properties. However, as AFSGs are a relatively new strategy, large-cohort studies are needed to assess their potential for wound healing. In addition, upcoming research should focus on novel strategies like network pharmacology [58], [59], nano-hydrogel based dressings [60], stem cell technology [61], and so on to develop new molecules and approaches to achieve accelerated wound healing.

References

1. R. Thakur, N. Jain, R. Pathak, and S. S. Sandhu, "Practices in wound healing studies of plants," *Evid Based Complement Alternat Med*, vol. 2011, 2011, DOI: 10.1155/2011/438056.
2. C. K. Sen, "Human Wound and Its Burden: Updated 2020 Compendium of Estimates," *https://home.liebertpub.com/wound*, vol. 10, no. 5, pp. 281–292, Mar. 2021, DOI: 10.1089/WOUND.2021.0026.
3. M. Baba, W. A. Davis, P. E. Norman, and T. M. E. Davis, "Temporal changes in the prevalence and associates of foot ulceration in type 2 diabetes: The Fremantle Diabetes Study," *J Diabetes Complications*, vol. 29, no. 3, pp. 356–361, Apr. 2015, DOI: 10.1016/J.JDIACOMP.2015.01.008.
4. D. G. ARMSTRONG, null D.P.M., and L. A. LAVERY, "Diabetic Foot Ulcers: Prevention, Diagnosis and Classification," *Am Fam Physician*, vol. 57, no. 6, pp. 1325–1332, Mar. 1998, Accessed: Nov. 17, 2022. [Online]. Available: https://www.aafp.org/pubs/afp/issues/1998/0315/p1325.html
5. M. Á. Tresierra-Ayala and A. García Rojas, "Association between peripheral arterial disease and diabetic foot ulcers in patients with diabetes mellitus type 2," *Medicina Universitaria*, vol. 19, no. 76, pp. 123–126, Jul. 2017, DOI: 10.1016/J.RMU.2017.07.002.
6. M. Asaf, N. Salim, M. Tuffaha, and N. A. Salim, "Challenging the Use of Bandage Compression as the Baseline for Evaluating the Healing Outcomes of Venous Leg Ulcer-Related Compression Therapies in the Community and Outpatient Setting: An Integrative Review," *Dubai Medical Journal*, vol. 1, no. 1–4, pp. 19–25, Nov. 2018, DOI: 10.1159/000494217.
7. J. Spiliotis *et al.*, "Wound dehiscence: is still a problem in the 21th century: a retrospective study," *World Journal of Emergency Surgery*, vol. 4, no. 1, p. 12, 2009, DOI: 10.1186/1749-7922-4-12.
8. V. K. Shukla, M. A. Ansari, and S. K. Gupta, "Wound healing research: A perspective from India," *International Journal of Lower Extremity Wounds*, vol. 4, no. 1, pp. 7–8, Mar. 2005, DOI: 10.1177/1534734604273660.
9. A. P. Veith, K. Henderson, A. Spencer, A. D. Sligar, and A. B. Baker, "Therapeutic strategies for enhancing angiogenesis in wound healing," *Adv Drug Deliv Rev*, vol. 146, pp. 97–125, Jun. 2019, DOI: 10.1016/j.addr.2018.09.010.
10. Y. Niu, Q. Li, Y. Ding, L. Dong, and C. Wang, "Engineered delivery strategies for enhanced control of growth factor activities in wound healing," *Adv Drug Deliv Rev*, vol. 146, pp. 190–208, Jun. 2019, DOI: 10.1016/j.addr.2018.06.002.
11. E. M. Tottoli, R. Dorati, I. Genta, E. Chiesa, S. Pisani, and B. Conti, "Skin Wound Healing Process and New Emerging Technologies for Skin Wound Care and Regeneration," *Pharmaceutics*, vol. 12, no. 8, p. 735, Aug. 2020, DOI: 10.3390/pharmaceutics12080735.

12. S. Jacobsen, "Topical Wound Treatments and Wound-Care Products," in *Equine Wound Management*, Wiley, 2016, pp. 75–103. DOI: 10.1002/9781118999219.ch5.
13. K. Barrigah-Benissan, J. Ory, A. Sotto, F. Salipante, J.-P. Lavigne, and P. Loubet, "Antiseptic Agents for Chronic Wounds: A Systematic Review," *Antibiotics*, vol. 11, no. 3, p. 350, Mar. 2022, DOI: 10.3390/antibiotics11030350.
14. M. Abd Elhakeem, N. Zaher, A. Ezzat, A. Ashraf, and O. Seif, "Methacrylate Powder Dressing in Traumatic, Pressure sore, Venous ulcers and Burn Wounds Healing," *Benha Medical Journal*, vol. 0, no. 0, pp. 0–0, Aug. 2022, DOI: 10.21608/bmfj.2022.128226.1560.
15. S. A. Chowdhry, "Use of oxidized regenerated cellulose (ORC)/collagen/silver-ORC dressings to help manage skin graft donor site wounds," *JPRAS Open*, vol. 22, pp. 33–40, Dec. 2019, DOI: 10.1016/j.jpra.2019.08.001.
16. E. B. Jude, J. Apelqvist, M. Spraul, and J. Martini, "Prospective randomized controlled study of Hydrofiber® dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers," *Diabetic Medicine*, vol. 24, no. 3, pp. 280–288, Mar. 2007, DOI: 10.1111/j.1464-5491.2007.02079.x.
17. P. Muangman, C. Pundee, S. Opasanon, and S. Muangman, "A prospective, randomized trial of silver containing hydrofiber dressing versus 1% silver sulfadiazine for the treatment of partial thickness burns," *Int Wound J*, vol. 7, no. 4, pp. 271–276, Aug. 2010, DOI: 10.1111/j.1742-481X.2010.00690.x.
18. R. G. Frykberg and J. Banks, "Challenges in the Treatment of Chronic Wounds," *Adv Wound Care (New Rochelle)*, vol. 4, no. 9, pp. 560–582, Sep. 2015, DOI: 10.1089/wound.2015.0635.
19. D.-C. Ding, Y.-H. Chang, W.-C. Shyu, and S.-Z. Lin, "Human Umbilical Cord Mesenchymal Stem Cells: A New Era for Stem Cell Therapy," *Cell Transplant*, vol. 24, no. 3, pp. 339–347, Mar. 2015, DOI: 10.3727/096368915X686841.
20. N. Kosaric, H. Kiwanuka, and G. C. Gurtner, "Stem cell therapies for wound healing," *Expert Opin Biol Ther*, vol. 19, no. 6, pp. 575–585, Jun. 2019, DOI: 10.1080/14712598.2019.1596257.
21. "Acellular Dermal Matrix (ADM) Products Used in Implant-Based Breast Reconstruction Differ in Complication Rates: FDA Safety Communication | FDA." Accessed: Nov. 18, 2022. [Online]. Available: https://www.fda.gov/medical-devices/safety-communications/acellular-dermal-matrix-adm-products-used-implant-based-breast-reconstruction-differ-complication
22. C. V. Ellis and D. A. Kulber, "Acellular Dermal Matrices in Hand Reconstruction," *Plast Reconstr Surg*, vol. 130, pp. 256S-269S, Nov. 2012, DOI: 10.1097/PRS.0b013e318265a5cf.
23. A. Pabst *et al.*, "Biomechanical Characterization of a New Acellular Dermal Matrix for Oral Soft Tissue Regeneration," *Journal of Investigative Surgery*, vol. 35, no. 6, pp. 1296–1303, Jun. 2022, DOI: 10.1080/08941939.2022.2047245.
24. T. H. Kim, J. H. Park, H. G. Jeong, and S. Y. Wee, "The Utility of Novel Fish-Skin Derived Acellular Dermal Matrix (Kerecis) as a Wound Dressing Material," *Journal of Wound Management and Research*, vol. 17, no. 1, pp. 39–47, Feb. 2021, DOI: 10.22467/JWMR.2020.01228.
25. T. O'Donnell, M. Passman, … W. M.-J. of vascular, and undefined 2014, "Management of venous leg ulcers: clinical practice guidelines of the Society for Vascular Surgery® and the American Venous Forum," *jvascsurg.org*, Accessed: Nov. 18, 2022. [Online]. Available: https://www.jvascsurg.org/article/S0741-5214(14)00851-9/abstract
26. S. Rakers *et al.*, "'Fish matters': the relevance of fish skin biology to investigative dermatology," *Exp Dermatol*, vol. 19, no. 4, pp. 313–324, Apr. 2010, DOI: 10.1111/j.1600-0625.2009.01059.x.
27. M. Sun, J. Dong, Y. Xia, and R. Shu, "Antibacterial activities of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) against planktonic and biofilm growing Streptococcus mutans," *Microb Pathog*, vol. 107, pp. 212–218, Jun. 2017, DOI: 10.1016/j.micpath.2017.03.040.
28. M. Sun, Z. Zhou, J. Dong, J. Zhang, Y. Xia, and R. Shu, "Antibacterial and antibiofilm activities of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) against periodontopathic bacteria," *Microb Pathog*, vol. 99, pp. 196–203, Oct. 2016, DOI: 10.1016/j.micpath.2016.08.025.
29. F. Bassetto, C. Scarpa, and F. Facchin, "Complicated Wounds," in *Textbook of Plastic and Reconstructive Surgery*, Cham: Springer International Publishing, 2022, pp. 27–38. DOI: 10.1007/978-3-030-82335-1_3.
30. M. L. B. Sørensen, R. B. Jansen, T. Wilbek Fabricius, B. Jørgensen, and O. L. Svendsen, "Healing of Diabetic Foot Ulcers in Patients Treated at the Copenhagen Wound Healing Center in 1999/2000 and in 2011/2012," *J Diabetes Res*, vol. 2019, pp. 1–9, Sep. 2019, DOI: 10.1155/2019/6429575.
31. A. C. Yelland *et al.*, "Impact of case-mix adjustment on observed variation in the healing of diabetic foot ulcers at 12-weeks using data from the National Diabetes Foot Care Audit of England and Wales: A cohort study," *Diabetic Medicine*, vol. 40, no. 1, Jan. 2023, DOI: 10.1111/dme.14959.
32. T. Zehnder and M. Blatti, "Faster Than Projected Healing in Chronic Venous and Diabetic Foot Ulcers When Treated with Intact Fish Skin Grafts Compared to Expected Healing Times for Standard of Care: An Outcome-Based Model from a Swiss Hospital," *International Journal of Lower Extremity Wounds*, 2022, DOI: 10.1177/15347346221096205.
33. B. Dorweiler *et al.*, "The marine Omega3 wound matrix for treatment of complicated wounds: A multicenter experience report," *Gefasschirurgie*, vol. 23, pp. 46–55, Aug. 2018, DOI: 10.1007/S00772-018-0428-2.
34. A. E. Rivera and J. M. Spencer, "Clinical aspects of full-thickness wound healing," *Clin Dermatol*, vol. 25, no. 1, pp. 39–48, Jan. 2007, DOI: 10.1016/j.clindermatol.2006.10.001.
35. T. Woodrow, T. Chant, and H. Chant, "Treatment of diabetic foot wounds with acellular fish skin graft rich in omega-3: a prospective evaluation," *https://DOI.org/10.12968/jowc.2019.28.2.76*, vol. 28, no. 2, pp. 76–80, Feb. 2019, DOI: 10.12968/JOWC.2019.28.2.76.
36. E. Lullove, B. Liden, … P. M.-… : a C. of, and undefined 2022, "Evaluating the effect of omega-3-rich fish skin in the treatment of chronic, nonresponsive diabetic foot ulcers: penultimate analysis of a multicenter, prospective," *europepmc.org*, Accessed: Nov. 29, 2022. [Online]. Available: https://europepmc.org/article/med/35797557
37. R. S. Kirsner *et al.*, "Fish skin grafts compared to human amnion/chorion membrane allografts: A double-blind, prospective, randomized clinical trial of acute wound healing," *Wiley Online Library*, vol. 28, no. 1, pp. 75–80, Jan. 2019, DOI: 10.1111/wrr.12761.
38. B. T. Baldursson, H. Kjartansson, F. Konrádsdóttir, P. Gudnason, G. F. Sigurjonsson, and S. H. Lund, "Healing rate and autoimmune safety of full-thickness wounds treated with fish skin acellular dermal matrix versus porcine small-intestine submucosa:

A noninferiority study," *International Journal of Lower Extremity Wounds*, vol. 14, no. 1, pp. 37–43, Mar. 2015, DOI: 10.1177/1534734615573661.

39. J. Yoon *et al.*, "Wound healing ability of acellular fish skin and bovine collagen grafts for split-thickness donor sites in burn patients: Characterization of acellular grafts and clinical," *Elsevier*, Accessed: Nov. 29, 2022. [Online]. Available: https://www.sciencedirect.com/science/article/pii/S0141813022002914
40. H. Luze, S. P. Nischwitz, C. Smolle, R. Zrim, and L.-P. Kamolz, "The Use of Acellular Fish Skin Grafts in Burn Wound Management—A Systematic Review," *Medicina (B Aires)*, vol. 58, no. 7, p. 912, Jul. 2022, DOI: 10.3390/medicina58070912.
41. S. Magnusson *et al.*, "Acellular Fish Skin Grafts and Pig Urinary Bladder Matrix Assessed in the Collagen-Induced Arthritis Mouse Model," *Int J Low Extrem Wounds*, vol. 17, no. 4, pp. 275–281, Dec. 2018, DOI: 10.1177/1534734618802899.
42. E. S. Mauer, E. A. Maxwell, C. J. Cocca, J. Ganjei, and D. Spector, "Acellular fish skin grafts for the management of wounds in dogs and cats: 17 cases (2019–2021)," *Am J Vet Res*, vol. 83, no. 2, pp. 188–192, Feb. 2022, DOI: 10.2460/ajvr.21.09.0140.
43. A. de Souza *et al.*, "Fish collagen for skin wound healing: a systematic review in experimental animal studies," *Cell Tissue Res*, vol. 388, no. 3, pp. 489–502, Jun. 2022, DOI: 10.1007/s00441-022-03625-w.
44. D. Li *et al.*, "Evaluation of a novel tilapia-skin acellular dermis matrix rationally processed for enhanced wound healing," *Materials Science and Engineering: C*, vol. 127, p. 112202, Aug. 2021, DOI: 10.1016/j.msec.2021.112202.
45. K. Lv, L. Wang, X. He, W. Li, L. Han, and S. Qin, "Application of Tilapia Skin Acellular Dermal Matrix to Induce Acute Skin Wound Repair in Rats," *Front Bioeng Biotechnol*, vol. 9, Feb. 2022, DOI: 10.3389/fbioe.2021.792344.
46. C. Winters, C. is P.-D. F. J, and undefined 2018, "Wound dehiscence on a diabetic patient with hemophilia and high risk of further amputation successfully healed with omega 3 rich fish skin: a case report," *diabetesonthenet.com*, vol. 21, no. 3, 2018, Accessed: Dec. 01, 2022. [Online]. Available: https://diabetesonthenet.com/wp-content/uploads/pdf/dotn5af79c6d5de192c212a36c077c19189a.pdf
47. K. Alam and S. L. A. Jeffery, "Acellular Fish Skin Grafts for Management of Split Thickness Donor Sites and Partial Thickness Burns: A Case Series," *Mil Med*, vol. 184, no. Supplement_1, pp. 16–20, Mar. 2019, DOI: 10.1093/MILMED/USY280.
48. C. Daidone, N. Salim, L. Smith, and A. Raza, "The Role of Fish Skin Xenografts in Healing Complex Wounds: A Brief Case Report," *Cureus*, Mar. 2024, DOI: 10.7759/cureus.56156.
49. latifi Rifat and Abbas Smiley, "acellelar fish skin garft use in open abdomen management," *Surgical Technology Internationsl*, vol. 42, 2023.
50. D. le Guellec, G. Morvan-Dubois, J. S.-I. J. of, and undefined 2003, "Skin development in bony fish with particular emphasis on collagen deposition in the dermis of the zebrafish (Danio rerio).," *ijdb.ehu.es*, vol. 48, pp. 217–231, 2004, Accessed: Dec. 01, 2022. [Online]. Available: http://www.ijdb.ehu.es/web/paper/15272388/skin-development-in-bony-fish-with-particular-emphasis-on-collagen-deposition-in-the-dermis-of-the-zebrafish-danio-rerio
51. S. R. Van Doren, "Matrix metalloproteinase interactions with collagen and elastin," *Matrix Biology*, vol. 44–46, pp. 224–231, May 2015, DOI: 10.1016/j.matbio.2015.01.005.
52. J. C. McDaniel, K. Massey, and A. Nicolaou, "Fish oil supplementation alters levels of lipid mediators of inflammation in microenvironment of acute human wounds," *Wound Repair and Regeneration*, vol. 19, no. 2, pp. 189–200, Mar. 2011, DOI: 10.1111/j.1524-475X.2010.00659.x.
53. S. Magnusson, B. Baldursson, … H. K.-M., and undefined 2017, "Regenerative and antibacterial properties of acellular fish skin grafts and human amnion/chorion membrane: implications for tissue preservation in combat casualty," *academic.oup.com*, Accessed: Dec. 01, 2022. [Online]. Available: https://academic.oup.com/milmed/article-abstract/182/suppl_1/383/4209412
54. E. Lima-Junior, N. Picollo, and M. Miranda, "Uso da pele de tilápia (Oreochromis niloticus), como curativo biológico oclusivo, no tratamento de queimaduras," *Rev Bras Queimaduras*, vol. 16, no. 1, pp. 10–17, 2017, Accessed: Dec. 01, 2022. [Online]. Available: https://repositorio.ufc.br/handle/riufc/28917
55. P. Brown, R. G. Will, R. Bradley, D. M. Asher, and L. Detwiler, "Bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease: background, evolution, and current concerns.," *Emerg Infect Dis*, vol. 7, no. 1, p. 6, 2001, DOI: 10.3201/EID0701.010102.
56. H. Kjartansson, I. Olafsson, … S. K.-O. J. of M., and undefined 2015, "Use of acellular fish skin for dura repair in an ovine model: a pilot study," *scirp.org*, Accessed: Dec. 01, 2022. [Online]. Available: https://www.scirp.org/html/4-2080131_60730.htm
57. C. Winters, R. S. Kirsner, D. J. Margolis, and J. C. Lantis, "Cost Effectiveness of Fish Skin Grafts Versus Standard of Care on Wound Healing of Chronic Diabetic Foot Ulcers: A Retrospective Comparative Cohort Study.," *Wounds*, vol. 32, no. 10, pp. 283–290, Oct. 2020.
58. S. Karhana, S. Dabral, A. Garg, A. Bano, N. Agarwal, and Mohd. A. Khan, "Network pharmacology and molecular docking analysis on potential molecular targets and mechanism of action of BRAF inhibitors for application in wound healing," *J Cell Biochem*, vol. 124, no. 7, pp. 1023–1039, Jul. 2023, DOI: 10.1002/jcb.30430.
59. A. Garg *et al.*, "Network pharmacology and molecular docking study-based approach to explore mechanism of benzimidazole-based anthelmintics for the treatment of lung cancer," *J Biomol Struct Dyn*, pp. 1–22, Sep. 2023, DOI: 10.1080/07391102.2023.2258419.
60. X. Zhang *et al.*, "Current Progress and Outlook of Nano-Based Hydrogel Dressings for Wound Healing," *Pharmaceutics*, vol. 15, no. 1, p. 68, Dec. 2022, DOI: 10.3390/pharmaceutics15010068.
61. N. Kosaric, H. Kiwanuka, and G. C. Gurtner, "Stem cell therapies for wound healing," *Expert Opin Biol Ther*, vol. 19, no. 6, pp. 575–585, Jun. 2019, DOI: 10.1080/14712598.2019.1596257.