Use of acellular fish skin grafts in wound healing: a literature review

KEY WORDS
- Burns
- Fish skin graft
- Skin graft
- Traumatic wounds
- Wound healing

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Background: Ideally, a good skin graft substitute should be readily available, cost-effective, have a low disease transmission risk, reduce infection and scarring, and aid wound healing. Fish skin grafts (FSG) are an accessible option to most populations. **Aim**: This literature review explores the use of FSG, as a xenograft, to aid in wound healing and the potential benefits or harms of using this intervention. **Methods**: A literature search using the PICO method was conducted on MEDLINE, CINAHL Plus, Cochrane Library, Web of Science and Embase, and hand searched on the Cardiff University Library. **Results:** FSG aided faster healing of burn wounds and reduced scarring. However, there was a lack of studies that examined the patient's experience and the long-term effects of FSG. **Conclusions**: FSG has multiple biological, economical and logistical benefits. It should be considered as an alternative graft option and has been shown to be useful in low resource environments. However, more robust research on the harms and benefits of FSG use is required.

Skin grafts are commonly used to aid wound closure in traumatic wounds from burns or combat. Autografts are ideal because they are harvested from the patient's own skin, which minimises the risk of rejection (Greenhalgh, 2019; Kogan et al, 2019; Fiakos et al, 2020). However, if the existing injury is extensive, as with a large burn, harvesting enough skin from a donor site can become difficult and cause donor site morbidity (Asuku et al, 2021). In that situation, alternative sources are considered, such as a human donor (allograft) or an animal skin graft (xenograft). Either approach temporarily substitutes the patient's skin to aid in the healing process until enough of their own skin can be used to cover their wounds (Magnusson et al, 2017; Singh et al, 2017). Allografts are considered after an autografts, however, they can be difficult to obtain and are required to undergo a lengthy and rigorous process to ensure that there is no risk of contamination or disease transmission (Magnusson et al, 2017).

Xenografts can come from many sources, with bovine collagen being most widely used historically (Heimbach et al, 1988; Uygur et al, 2008; Yoon et al. 2022). However, despite the positive results from bovine-based xenografts (Heimbach et al, 1988; Uygur et al, 2008; Yoon et al, 2022), some patients refuse to receive a possibly lifesaving treatment because of their cultural beliefs (Grabenstein, 2013). Bovine products also have the potential to carry harmful diseases that could infect humans (Wenz et al, 2001).

A good skin graft substitute should be readily available, cost-effective, have low risk of disease transmission, reduce infection and scarring, and be effective at helping heal the wound (Kogan et al, 2019; Stone et al, 2021; Luze et al, 2022). Fish skin grafts (FSG) have recently become of interest as a xenograft with two main species being assessed: Nile Tilapia and North Atlantic cod. Because both originate from different areas of the world, FSG is an accessible option to most populations (Luze et al, 2022).

METHODS

A review of the literature was conducted on MEDLINE, CINAHL Plus, Cochrane Library, Web of Science, and Embase databases, and hand

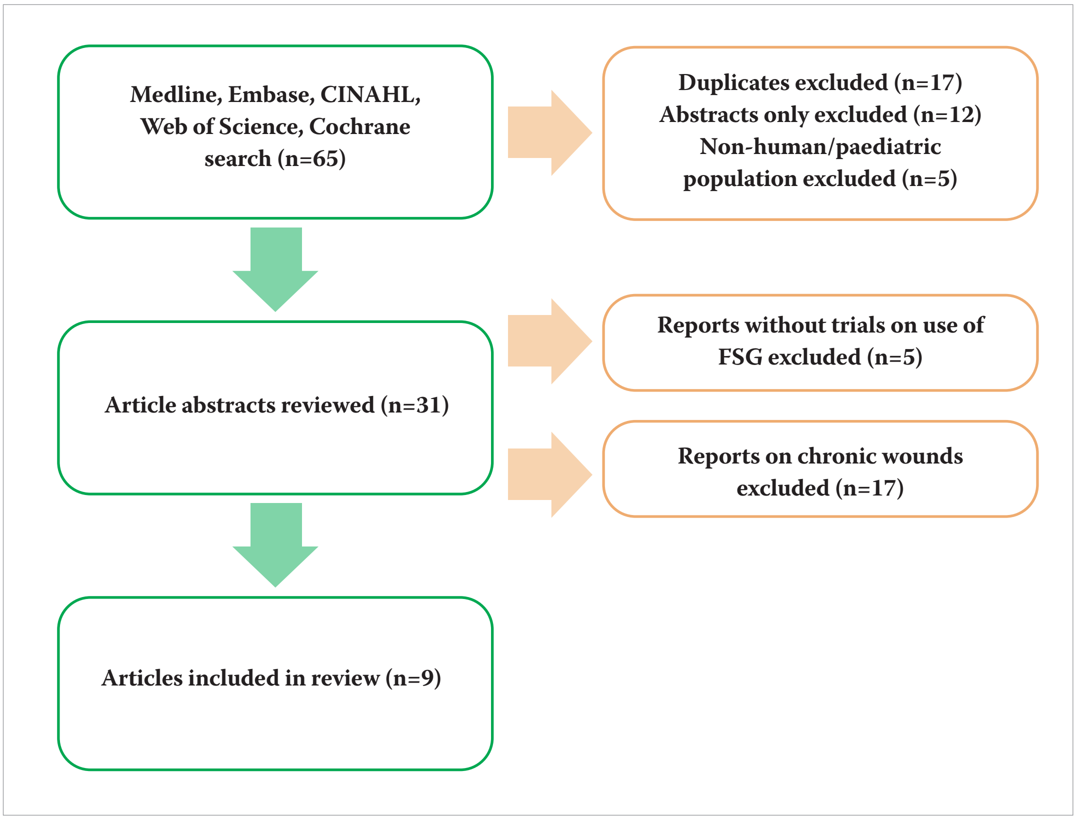

Figure 1. Literature review process

searched on the Cardiff University Library using the PICO framework:

- P (Person or Problem): adult human patients who have acute wounds
- I (Intervention): acellular fish skin grafts
- C (Comparison): conventional dressings and other graft types
- O (Outcome): benefits and harms of acellular fish skin graft use.

Key words used in the search included acellular fish skin, split-thickness skin graft (STSG), wound healing, wound management and burns. Evidence for FSG is relatively new, therefore, most research has been completed and published in the last eight years. Since there is limited evidence available, research on both animal and human models was included. All articles included were in English. Only acute wounds were included in the review (ie. no chronic wounds, such as diabetic foot ulcers), and studies must have completed trials on how the use of FSG. Figure 1 shows the number of papers reported for each stage of the review process.

Proposed benefits of fish skin grafts

Fish skin grafts are considered an option for wound healing for the following reasons: Omega-3 fatty acid content, relatively gentle preservation process, ideal cellular structure and a smaller disease transmission risk compared with allografts and other xenografts (Hu et al, 2017; Luze et al, 2022). Omega-3 fatty acids have anti-inflammatory properties (Lands, 2005) and possibly help transition a wound from the inflammatory stage to the proliferation stage (Serhan, 2014). The process of preparing FSG is also gentle enough to preserve these omega-3 fatty acids and the structure of the fish skin, while still being treated enough to prevent disease transmission (Magnusson et al, 2017; Dorweiler et al, 2018). This contrasts with bovine or porcine-derived grafts, which require a lengthier preservation process that often denaturises the matrices and removes a large portion of the collagen that could help with wound healing (Magnusson et al, 2017; Dorweiler et al, 2018). Depending on the method of FSG preparation, it is possible that the FSG can be stored at room temperature for up to three years (Alam and Jeffery, 2019), making it a more accessible product, particularly in resource-poor areas, such as combat zones or low to middle-income countries (Lima et al, 2020).

The structure of FSG was found to be beneficial as it is more porous than dehydrated human amnion/chorion membrane allograft (dHACM), 16.7 holes versus 1.7 holes per 100μm on average (Magnusson et al, 2017). These holes allow fibroblasts and keratinocytes to pass through and aid wound healing (Dorweiler et al, 2018). In addition to having a lower disease transmission risk, FSG has antibacterial properties that last 48–72 hours due to its omega-3 fatty acid content (Mil-Homens et al, 2012; Magnusson et al, 2017).

Preclinical evidence for fish skin grafts

In 2017, Hu and colleagues compared the use of Nile Tilapia skin with burn ointment and with no treatment strategies for scald burns on rabbits. Their study showed that on day 11 post-injury, wound healing was faster in the rabbits who received marine collagen peptides (MCP) from tilapia skin when compared with the positive control group (38.8% versus 19.5% of wounds healed, $p<0.05$) and the no treatment control group (8.7%, $p<0.05$) (Hu et al. 2017). They also noted, through histological evaluation, that the wounds that received MCP treatment had more new epidermis and granulation tissue, whereas the positive control and no treatment group had very little proliferation and new epidermis formed. Although these results cannot be generalised to the human population because rabbit skin does not resemble human skin (Sami et al, 2019), the study demonstrated that MCP from tilapia had promising results in helping heal burn wounds.

Stone and colleagues (2021) also studied the effects of FSG from Atlantic cod and compared it with foetal bovine dermis on deep partial-thickness burns on Yorkshire pigs. The authors noted that both FSG and foetal bovine dermis were easy to apply and did not seem to result in any wound infections. Re-epithelialisation was determined using the computer software, SilhouetteConnect, (Aranz Medical), which showed significantly faster healing on day 14 for the FSG group compared with the foetal bovine dermis (50.2% versus 23.5%, of wound healed, $p<0.05$), and wound size had decreased more on day 14 (FSG 93.1% versus foetal bovine dermis; 106.7%; respectively, $p<0.05$). They also noted more blood flow to the wounds with the FSG on day 14 (4.9 versus 3.1-fold change increase in blood flow; $p<0.05$) via laser speckle imaging (LSI, Moor Instruments Inc.). In this study, using photographs with digital planimetry to assess wound healing rates reduces the potential for observer bias, and increases validity and reliability compared with subjective assessments (Wendelken, et al, 2011). Laser speckle imaging is a valid, reliable and non-invasive tool that is commonly used to assess skin perfusion.(Wilkinson et al, 2018).

The results of Stone et al (2021) favoured towards the use of FSG as a substitute for foetal bovine dermis in the healing of deep partial-thickness burns, however, it was noted that human wounds heal differently than animals, and therefore the results of the study would not be generalisable to humans. However, the preclinical studies of Hu et al and Stone et al indicated that FSG has the potential to aid in the healing of acute wounds on humans.

Clinical evidence for fish skin grafts

Alam and Jeffery's (2019) case series on the use of FSG on human donor graft sites showed equally positive results. They found that the FSG (Kerecis Omega3 Wound, Kerecis Ltd.) took approximately 10–16 days for the site to fully re-epithelialise, and had no infection, no adverse reactions and reduced pain. The authors applied FSG on partial-thickness burns (a cooking-oil burn to the thigh and a flame injury to the hand), both of which healed within two weeks and showed minimal scarring and little colour change to the healed skin (Alam and Jeffery, 2019). The case series included 10 patients for the donor site study, with donor site size varying from $40cm^2$ to $950cm^2$, and age ranges of 19–80 years. The small sample size and the wide variety of patient demographics may have accounted for the variability of the time it took to heal the wound, making it difficult to determine how the fish skin itself assisted with wound healing. The sample size for the partial-thickness burns would also be too small to be considered statistically significant.

Nevertheless, the lack of infection, the ease of use of the FSG and the comfort it gave the patients are valuable reports to further support the possible use of FSG in wound healing (Alam and Jeffery, 2019). FSG could also potentially assist the healing of donor site wounds and accelerate the availability of autografts for re-harvesting.

Yoon and colleagues (2022) compared the effects a bovine collagen graft (BCG; ProHeal Collagen Wound Dressing, MedSkin Solutions) with an FSG (Kerecis Omega3 Wound, Kerecis Ltd.) on graft donor sites. This was done by placing one piece of the BCG product on one half of the donor site, and another piece of the FSG product on the other half for one cohort (n=26). For control purposes, a second cohort (n=26) had one piece of the FSG on one half of a donor site and nothing on the other half.

The results showed that the FSG on the donor site healed approximately four days faster than no treatment, and approximately two days faster when compared with the BCG product (p<0.05; Yoon et al, 2022). Imaging software (ImageJ, National Institutes of Health) as well as two burn surgeons evaluated the healing rates of the wounds from photographs and recorded mean values. The use of the software supplemented the inter-rater reliability of the surgeons' assessment.

Despite these promising results, there were several limitations to the study methods. The authors did not specify if the participants were randomly assigned to each cohort and therefore it can not be considered a randomised control trial (RCT). This would have provided more confidence that the outcomes were due to the products used, and not influenced by confounding factors. The preparation of the products was also different with the FSG being hydrated before use, and the BCG not. The FSG and the BCG also differed in their absorption of water, which could have affected the results of the study. The BCG absorbed significantly more water than the FSG after rehydration (2059.1% versus 302.8% of water absorbed; p<0.05), while the FSG had significantly more ultimate tensile strength when wet compared with the BCG2 (10.1MPa versus 0.047MPa; p<0.05). The ability to absorb more water could potentially have allowed for better maintenance of a moist wound bed, which could encourage new tissue to granulate and re-epithelialisation (Winter, 1962). This could make BCG falsely more advantageous, causing a performance bias. Yoon and colleagues (2022) also noted that patient comorbidities were not considered, which could have also affected the results as many intrinsic and extrinsic factors can affect wound healing (Guo and DiPietro, 2010). With a total of 52 participants, it was unclear if there was enough power in the study to detect true effect. Nevertheless, the results appeared to corroborate previous studies that FSG were just as effective as bovine products, if not slightly better in terms of healing times (Stone et al, 2021; Yoon et al, 2022). There was no conflict of interest declared, and none of the authors were associated with Keresis Ltd, reducing possible industry sponsorship bias.

Kirsner and colleagues (2020) examined whether FSG could be an equal, if not superior, alternative to dehydrated human amnion/chorion membrane (dHACM; EpiFix, MiMedx Group Inc.). In their double-blinded RCT, they included 85 healthy volunteers and treated 170 wounds — two 4mm punch biopsies were created on the same forearm of each patient, then they compared the amount of time required to heal the wounds after receiving FSG to one wound, and dHACM to the other. At day 28 of treatment, the authors evaluated pain, erythema, infection, and cost of products used. The results showed that wounds treated with the FSG (Kerecis Omega3 Wound, Kerecis Ltd.) healed faster with a hazard ratio of 2.37 (95% confidence interval [CI]: 1.75–3.21; p<0.05), indicating a strong statistically significant positive correlation. However, it would have been more useful to know how many days faster the FSG healed than the dHACM to make the findings clinically relevant.

The methodology of this study was well reported and clearly outlined a study design with participants being without comorbidities, such as peripheral vascular disease or on medications such as systemic corticosteroids that could affect wound healing (Guo and DiPietro, 2010). All patients received both treatments, one on each wound and, therefore, acted as their own control. Each wound was randomised to the treatment it received; only the trial physician knew. Both the patient and the evaluating physician were blinded to the randomisation. To further support the results, three other reviewers examined the photographs of the wounds independently to determine when wound closure occurred. However, since wound closure can be a subjective observation, and clear criteria of what would be considered complete wound closure was not discussed, the inter-rater reliability may have been compromised.

Use of technology to analyse wound closure may have been beneficial to the study and enhance the reliability of the result obtained. Kirsner and colleagues (2020) found that using the dHACM product was 76% more expensive than the FSG ($p<0.05$). The authors also noted that the location of the wound was not a factor in wound healing ($p>0.05$), which was important to note, as different areas of the body can heal at different rates. For example, wounds that occur intra-orally were found to heal faster due to fibroblasts being able to reorganise the surrounding extracellular matrix more efficiently (Stephens et al, 1996).

Limitations of the study included lack of generalisability as the cohort studied was 99% Caucasian and only acute wounds were studied. There is also potential sponsorship bias as some of the authors were also stakeholders in Keresis Ltd. or paid consultants of the company, and it was not clear if those authors were involved in the evaluation of the results. However, because the methodology included double-blinding and with several different independent evaluators, this should have addressed the potential sponsorship bias.

Recently, Reda and colleagues (2023) documented the use of FSG in the management of combat injuries in challenging and unforgiving environments. They found it very user friendly, light in weight, easy to transport, did not require any other tools or equipment to apply and required minimal training to use. After application of the FSG, the authors also noted that granulation occurred in days, and in some cases weeks sooner than standard dressings, which consequentially allowed for less interventions and avoided the need for flap surgery. There was no assessment of the wound pre-application of the FSG due to the nature of the presenting patients, and the treatment provided included the use of negative pressure wound therapy (NPWT) after the application of the FSG. This resulted in another variable, therefore, it was difficult to ascertain how much of the results were due to FSG use. However, Reda and colleagues (2023) demonstrated the positive effects FSG can have on providing treatment at point of care, which is invaluable in war zone where sterile environments are rare and time is of the essence.

Harms and further investigations

The risk of allergies or sensitivities to an ingredient is the primary indication to restrict the use of a product as it can cause harm to the patient. In Kirsner and colleague's study (2020), 22% of participants (n=19) complained of puritus to the periwound where the FSG was in contact with the skin, and 8% (n=7) developed a minor rash. A finding from Alam and Jeffery's 2019 study was that the odour produced by the FSG was reported to affect an individual's appetite and perception of self.

Scar formation is an area of interest due to both aesthetic and skin integrity concerns. Scars can appear like deformities, which can affect patients' self-esteem, leading to potentially public isolation to avoid embarrassment due to negative stigmas (Brown et al, 2008). Physiologically, patients have reported that their scars caused itching, discomfort and pain (Mauck et al, 2018), as well as restriction in movement if they are located over a joint due to contractures (Deflorin et al, 2020).

Varon and colleagues' 2022 study on different topical off-the-shelf therapies included FSG and investigated the scar elevation index (SEI) after the healing of deep partial-thickness burns conducted on pigs. SEI was considered a valid and reliable and appropriate tool (Tandara and Mustoe, 2008; Mousavizadeh et al, 2021). The results showed that FSG had the lowest SEI measurement (1.15±0.06) compared with other products (silver sulfadiazine (SSD), irradiated sterile human skin allograft (IHS), biodegradable temporizing matrix, polylactic acid skin substitute (PLA), and hyaluronic acid ester matrix (HAM)). However, the results were only statistically significant ($p<0.05$) when comparing FSG with biodegradable temporizing matrix and it is unclear if the sample size was large enough to provide 80% power. Conversely, robust studies on the effects a product could have on scarring would be difficult to conduct due to many variable factors, such as the anatomical location of the wound, the aetiology of the wound, the type of scar and patient demographics (Sidgwick et al, 2015).

There appears to be no other reported risk factors to using FSG to aid in the healing of wounds. Nevertheless, larger scale studies are required to identify whether more harms to patient outcome can be identified (Luze et al, 2022). Further investigations using human models would also be beneficial in obtaining more accurate results and identifying any other harms. However, this can be challenging as it is difficult to control for the multitude of variables that occur with acute injuries, such as comorbidities and extent of injuries, and it could be unethical to continuously conduct trials that require intentionally injuring a patient.

CONCLUSION

Fish skin grafts are a relatively new development in xenograft options, however, the recent evidence has shown that it is a viable option to aid acute wound healing, specifically donor sites and in some cases, burns (Luze et al, 2022). There still needs to be more robust evaluation of the product as most of the evidence presented are case studies/series or have sample sizes that do not have enough power (Luze et al, 2022). However, based on the benefits that have been highlighted and the minimal harm demonstrated so far, FSG seems to be an effective alternative to the other xenografts available. Its longer shelf life, relatively gentle processing, healing and antibacterial properties (Lands, 2005; Magnusson et al, 2017), less risk of disease transmission, and significantly less cost compared to other xenografts (Kirsner et al, 2020) making it more appealing for health professionals to use FSG to aid wound healing. However, current gaps in the evidence include possible complications, such as infection or odour, and other long-term effects of FSG use, such as scarring and quality of new tissue formed. It would also be valuable to have more investigations on the use of FSG compared with other xenografts in terms of ease of use, cost, healing rates and potential harm. WUK

Declaration of interests

The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

Alam K, Jeffery SLA (2019) Acellular fish skin grafts for management of split thickness donor sites and partial thickness burns: a case series. *Mil Med* 184(Suppl 1):16–20. https://doi.org/10.1093/milmed/usy280

Asuku M, Yu TC, Yan Q et al (2021) Split-thickness skin graft donor-site morbidity: a systematic literature review. *Burns* 47(7):1525–46. https://doi.org/10.1016/j.burns.2021.02.014

Brown BC, McKenna SP, Siddhi K et al (2008) The hidden cost of skin scars: quality of life after skin scarring. *J Plast Reconstr Aesthet Surg* 61(9):1049–58. https://doi.org/10.1016/j.bjps.2008.03.020

Deflorin C, Hohenauer E, Stoop R et al (2020) Physical management of scar tissue: A systematic review and meta-analysis. *J Altern Complement Med* 26(10):854–65. https://doi.org/10.1089/acm.2020.0109

Dorweiler B, Trinh TT, Dünschede F et al (2018) The marine Omega3 wound matrix for treatment of complicated wounds: a multicenter experience report. *Gefasschirurgie* 23(Suppl 2):46–55. https://doi.org/10.1007/s00772-018-0428-2

Fiakos G, Kuang Z, Lo E (2020) Improved skin regeneration with acellular fish skin grafts. *Engineered Regeneration* 1:95–101 https://doi.org/10.1016/j.engreg.2020.09.002

Grabenstein JD (2013) What the World's religions teach, applied to vaccines and immune globulins. *Vaccine* 31(16). https://doi.org/10.1016/j.vaccine.2013.02.026

Greenhalgh DG (2019) Management of Burns. *N Engl J Med* 380(24):2349–59. https://doi.org/10.1056/nejmra1807442

Guo S, DiPietro LA (2010) Critical review in oral biology & medicine: Factors affecting wound healing. *J Dent Res* 89(3):219–29. https://doi.org/10.1177/0022034509359125.

Heimbach D, Luterman A, Burke J et al (1988) Artificial dermis for major burns. A multi-center randomized clinical trial. *Ann Surg* 208(3):313–20. https://doi.org/10.1097%2F00000658-198809000-00008

Hu Z, Yang P, Zhou C et al (2017) Marine collagen peptides from the skin of Nile Tilapia (Oreochromis niloticus): characterization and wound healing evaluation. *Mar Drugs* 15(4):102. https://doi.org/10.3390/md15040102

Kirsner RS, Margolis DJ, Baldursson BT et al (2020) Fish skin grafts compared to human amnion/chorion membrane allografts: a double-blind, prospective, randomized clinical trial of acute wound healing. *Wound Repair Regen* 28(1):75–80. https://doi.org/10.1111%2Fwrr.12761

Kobayashi N, Toshiya M, Reiko T et al (2013) Comparison of wound healing rate and time to complete wound healing according to wound location in critical limb ischemia. *Journal of the American College of Cardiology* 61(10): E2105. https://doi.org/10.1016/s0735-1097(13)62105-1.

Kogan S, Halsey J, Agag RL (2019) Biologics in acute burn injury. *Ann Plast Surg* 83(1):26–33. https://doi.org/10.1097/sap.0000000000001915

Lands WEM (2005) Fish, Omega-3 and Human Health, 2nd Edn. https://doi.org/10.4324/9781003002284, AOCS Publishing

Lima EM, de Moraes Filho MO, Costa BA et al (2020) Lyophilised tilapia skin as a xenograft for superficial partial thickness burns: A novel preparation and storage technique. *J Wound Care* 29(10):598–602. https://doi.org/10.12968/jowc.2020.29.10.598

Luze H, Nischwitz SP, Smolle C et al (2022) The use of acellular fish skin grafts in burn wound management—a systematic review. *Medicina (Kaunas)* 58(7):912. https://doi.org/10.3390%2Fmedicina58070912

Magnusson S, Baldursson BT, Kjartansson H et al (2017) Regenerative and antibacterial properties of acellular fish skin grafts and human amnion/chorion membrane: Implications for tissue preservation in combat casualty care. *Mil Med* 182(S1):383–8. https://doi.org/10.7205/milmed-d-16-00142

Mauck MC, Shupp JW, Williams F et al (2018) Hypertrophic scar severity at autograft sites is associated with increased pain and itch after major

thermal burn injury. *J Burn Care Res* 39(4). doi: 10.1093/jbcr/irx012.
Mil-Homens D, Bernardes N, Fialho AM (2012) The antibacterial properties of docosahexaenoic omega-3 fatty acid against the cystic fibrosis multiresistant pathogen Burkholderia cenocepacia. *FEMS Microbiol Lett* 328(1):61–9. https://doi.org/10.1111/j.1574-6968.2011.02476.x
Mousavizadeh SM, Torbati PM, Daryani A (2021) The effects of kiwifruit dressing on hypertrophic scars in a rabbit ear model. *J Wound Care* 30(Sup9a):XVi-XVvii. https://doi.org/10.12968/jowc.2021.30.sup9a.xv
Reda F, Kjartansson H, Jeffery SLA (2023) Use of fish skin graft in management of combat injuries following military drone assaults in field-like hospital conditions. *Mil Med* https://doi.org/10.1093/milmed/usad028
Sami DG, Heiba HH, Abdellatif A (2019) Wound healing models: A systematic review of animal and non-animal models. *Wound Medicine* 24(1):8–17. https://doi.org/10.1016/j.wndm.2018.12.001
Serhan CN (2014) Pro-resolving lipid mediators are leads for resolution physiology. *Nature* 510(7503):92–101. https://doi.org/10.1038/nature13479
Sidgwick GP, McGeorge D, Bayat A (2015) A comprehensive evidence-based review on the role of topicals and dressings in the management of skin scarring. *Arch Dermatol Res* 307(6):461–77. https://doi.org/10.1007/s00403-015-1572-0
Singh M, Nuutila K, Collins KC, Huang A (2017) Evolution of skin grafting for treatment of burns: Reverdin pinch grafting to Tanner mesh grafting and beyond. *Burns* 43(6):1149–54..https://doi.org/10.1016/j.burns.2017.01.015
Stephens P, Davies KJ, Al-Khateeb T et al (1996) A comparison of the ability of intra-oral and extra-oral fibroblasts to stimulate extracellular matrix reorganization in a model of wound contraction. *J Dent Res* 75(6):1358-64. https://doi.org/10.1177/00220345960750060601
Stone R, Saathoff EC, Larson DA et al (2021) Accelerated wound closure of deep partial thickness burns with acellular fish skin graft. *Int J Mol Sci* 22(4):1590. https://doi.org/10.3390%2Fijms22041590
Tandara AA, Mustoe TA (2008) The role of the epidermis in the control of scarring: evidence for mechanism of action for silicone gel. *J Plast Reconstr Aesthet Surg* 61(10):1219–25. https://doi.org/10.1016/j.bjps.2008.03.022
Uygur F, Evinc R, Ulkur E, Celikoz B (2008) Use of lyophilized bovine collagen for split-thickness skin graft donor site management. *Burns* 34(7):1011–4. https://doi.org/10.1016/j.burns.2007.12.007
Varon DE, Anders H Carlsson AH, Cooper LE et al. 2022. Evaluation of topical off-the-shelf therapies to improve burn wound healing during prolonged field care. *Mil Med* 188(9-10):3034–44. https://doi.org/10.1093/milmed/usac114
Wendelken ME, Berg WT, Lichtenstein P et al (2011) Wounds measured from digital photographs using photodigital planimetry software: validation and rater reliability. *Wounds* 23(9):267–75
Wenz B, Oesch B, Horst M (2001) Analysis of the risk of transmitting bovine spongiform encephalopathy through bone grafts derived from bovine bone. *Biomaterials* 22(12):1599–606. https://doi.org/10.1016/s0142-9612(00)00312-4
Wilkinson JD, Leggett SA, Marjanovic EJ et al (2018) A multicenter study of the validity and reliability of responses to hand cold challenge as measured by laser speckle contrast imaging and thermography. *Arthritis Rheumatol* 70(6):903–11. https://doi.org/10.1002%2Fart.40457
Winter GD (1962) Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic Pig. *Nature (London)* 193(4812):293–4. https://doi.org/10.1038/193293a0
Yoon J, Yoon D, Lee H et al (2022) 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 application. *Int J Biol Macromol* 205:452–61. https://doi.org/10.1016/j.ijbiomac.2022.02.055