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Utilizing tilapia fish skin biomaterial for burn wound dressing: A systematic review

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ABSTRACT

Burn wound management remains a burden in our hospitals with more than 180,000 people dying annually due to burn-related complications. Bacterial infections further affect the healing duration of the wound hence most treatment modalities have aimed at maintaining aseptic conditions on the wound. Silver sulphadiazine (SSD) cream 1 % has demonstrated the ability to bind to bacteria cell walls, its amino acids and DNA, and interferes with its respiratory chain resulting in bacteria death. SSD is considered the gold standard treatment of burn wounds despite its shortfalls in the treatment of burns. As a result, recent studies have focused on finding better burn treatment alternatives. Traditional wound dressings like gauze, lint, bandages, and cotton wool are being replaced by modern wound dressings like hydrogels, alginates, and membranes. Despite that these modern dressings provide a moist environment to necessitate wound healing, they also have disadvantages including limited exudate absorptive capacity and lack of antimicrobial effect. Alternatively, the use of tilapia fish skin biomaterial has gained interest over the past years in the treatment of burn wounds. Its usage has been attributed to its high percent composition of collagen type I and III and its ability to influence cell proliferation, differentiation, migration, and synthesis of other proteins on the wound site. In this review, we focus on the various roles that the tilapia fish skin has played in burn wound treatment applications. We discuss how the tilapia fish skin biomaterial has been tailored to be used in different forms of wound dressings and how its processed products have been utilized in treating burns. In this review, we also make a proposition on how the tilapia fish skin biomaterial can be enhanced to be an effective treatment modality for burn wounds.

Introduction

According to the World Health Organisation (WHO), burns account for more than 180,000 deaths annually across the globe while those that survive are subjected to prolonged hospitalization, loss of function of the affected area, as well as deformities and disabilities in extreme cases [1]. The severity of burns arises from the wound bed which is a moist, warm, and nutritious environment that provides favourable conditions for microbial growth, which consequently predisposes the wound to infections [2]. Usage of biological agents

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has been reported to be effective in modifying aspects of wound healing and exhibiting potential in guiding the process of wound healing [3]. Currently, the treatment and management modalities of burns aim at maintaining aseptic conditions on the wound, to allow for cell and tissue regeneration, which eventually leads to wound healing [4]. The available methods in burn wound treatment still face some challenges in achieving the best outcomes in the healing process of the burns.

Silver sulphadiazine (SSD) cream 1 % is presently the most common treatment for burns in various hospitals around the world. The mechanism of action for SSD has led to its widespread success in treating burns as a topical antimicrobial cream. The silver in SSD binds to the bacterial cell walls, amino acids and DNA, and interferes with respiratory chain of bacteria [5]. Ulkür et al. [6] reported that the binding of silver ions to the DNA of the microbes leads to the release of sulfonamide which consequently kills the microbes. The ability to bind to these different target sites broadens the antimicrobial effect and results in low resistance rates of the bacteria to SSD. As for sulphadiazine, albeit it being an antibiotic, its incorporation in the SSD is mainly due to the specific synergetic effect in combination with sub-inhibitory levels of silver rather than acting as an antibacterial agent alone [7]. Despite SSD registering all these successes in the treatment of burns, incidences of keloid and hypertrophic scarring with significant impairment of function [8], necrosis and ischemia [9] have been reported to be quite high amongst cases treated with silver sulphadiazine over the years. Research has also revealed that, the application of SSD in treating burns results in the creation of a pseudo-eschar layer which makes it difficult to evaluate the wound depth and healing status of the wound [10]. Besides these, the use of SSD has demonstrated cytotoxicity effects on epidermal cells with hair follicle death that result in decreased healing rate and increased skin problems once the wound heals [11]. Due to such findings, recent research studies have focused on finding a better alternative treatment protocol for burns.

Apart from SSD, other treatment methods that are being used in hospitals to treat burn wounds. Some traditional wound dressing products like gauze, lint, natural or synthetic bandages, and cotton wool are still being used in some hospitals as primary or secondary wound dressings [12]. The advantages of these wound dressings are that they are inexpensive, readily available and they help with wound drainage. On the other hand, these wound dressings tend to adhere to the wound as they dry leading to traumatic and painful removal [12]. They also must be changed frequently making them costly and pose a risk of repetitive tissue damage [13]. Due to these deficiencies, these dressings have mostly been replaced with modern wound dressings that are able to provide a moist environment on the wound for easy healing.

Modern wound dressings are mostly based on synthetic polymers, and they can be grouped into hydrogels, alginates, hydrocolloids, films/membranes, and foams [12,13]. Hydrogels are mostly made from synthetic cross-linked polymer components (mainly methacrylate and polyvinyl pyrrolidone) that make the material insoluble with water dispersion medium (70–90 % of water content) [14]. The high-water content of hydrogels keeps the wound bed in moist environment and reduces the temperature around the wound; its rubbery nature with a low interfacial tension result in better biocompatibility, non-irritant nature, and reduced inflammation [12,14]. On the other hand, alginate is a natural polysaccharide derived from seaweed that is composed of two uronic acids in linear chains that interact with calcium to produce calcium alginate [12,15,16] which has excellent water-absorbing capabilities, biodegradable, and is biocompatible [16,17]. As for hydrocolloids, they are one of the most widely used modern wound dressing that has also been widely studied. Hydrocolloids have two layers (inner colloidal layer and outer water-impermeable layer) and they are made up of gel forming materials and adhesives [12,13]. Despite providing a moist environment for healing on the wound, these modern wound dressings also have their own shortfalls. Hydrogels have a limited absorptive capacity because they already have a high-water content as such their applications on highly exudating wounds is reduced just like hydrocolloids [18]. As for alginates, despite that they can be used in medium to high exudating wounds, they are not recommended for dry wounds, third-degree burn wounds, and wounds with eschar [11].

In a review by Yeung and Kelly [19], collagen was reported to be critical in aiding tissue regeneration in a wound. Collagen is a principal component of extracellular matrix (ECM) of body tissues, and it is the most abundant protein in mammals. It forms a key component of the dermis which is the second layer of the human skin [20]. Besides being a structural scaffold in tissues, collagen has also been reported to be influential in various cellular functions that occur on a wound, such as cell proliferation, differentiation, migration, and synthesis of other proteins [21]. After an injury to the skin tissue, the activation and aggregation of platelets is induced by the collagen, thereby resulting in fibrin deposition which eventually results in the formation of a clot. Simultaneously, the degradation of collagen liberates some fragments which promote the proliferation of fibroblasts and the synthesis of growth factors, which aid angiogenesis and re-epithelialization [22]. Collagen type III is laid down first in the early stages of wound healing while the proportion of collagen type I increases as the healing process progresses towards scar formation and wound remodeling which eventually increases the tensile strength of the wound [23]. The involvement of collagen in all these crucial processes in wound healing has seen collagen being utilized as an adjunct burn wound treatment to foster the wound healing process. Furthermore, it's biocompatibility [24], low immunogenicity, ability to recruit macrophages and fibroblast, and its ease of application has enabled collagen-based biomaterials to be used in wound dressing applications [25,26]. This explains as to why recent research studies on burns treatment have focused on collagen-based biomaterials. The tilapia fish skin has been reported to be very rich in collagen type I and III. No wonder tilapia fish skin-based biomaterials are currently being researched on their potential to replace the use of silver sulphadiazine cream 1 % in treating burns.

Several studies have reported how effective the fish skin has been in wound healing applications. Out of the different fish species out there, the tilapia fish has been at the center of such research discoveries. These studies have used the tilapia fish skin either in their raw form as a xenograft biomaterial or in a processed form as macromolecules extracted from it. Despite that studies have reported that tilapia fish skin aids wound healing, there is lack of published papers that have summarized the various forms of tilapia fish skin biomaterial that can be used in wound healing applications. Apparently, absence of literature that consolidates the different approaches of utilizing tilapia fish skin biomaterial in burn wound dressing necessitated the need for a review paper. This review paper, therefore, discusses the role of tilapia fish skin biomaterial in the healing process of burn wounds. The paper aims to highlight various

designs that tilapia fish skin can exhibit in wound healing applications. By consolidating published results on the application of tilapia fish skin biomaterial in burn wound treatment, this paper will lessen the burden for researchers who are interested in optimizing the processing and characterization methods for the usage of tilapia fish skin biomaterial in burn wound applications. Researchers have processed the tilapia fish skin biomaterial into different products that have been utilized in the healing process of burn wounds. Recent literature on the application of tilapia fish skin as a burn wound dressing biomaterial in the treatment of burns are hereby summarized.

The current research trend to find a better alternative to SSD as the burn wound dressing gold standard in the hospitals motivated the authors to write this review paper. The primary function of a wound dressing has evolved over the past decades from simply keeping the wound dry and preventing the entry of pathogenic bacteria on the wound, to providing a conducive environment on the wound for the healing process [13]. Such optimum conditions for effective wound healing include a moist environment, effective oxygen circulation on the wound, and aiding cellular regenerative processes that will eventually result in wound healing. Although researchers have been successful in developing wound dressings from natural and synthetic materials that provide optimum conditions for wound healing, there is still a need to develop wound dressings that can greatly reduce the wound healing process as well as decrease the risk of hypertrophic scarring and loss of function of the affected area. This review examines how the tilapia fish skin biomaterial has been utilized in various research studies on wound healing. The potential benefit of utilizing tilapia fish skin in wound healing has greatly been emphasized alongside the possible future directions of its use in wound healing applications.

Methodology

Review protocol

The systematic review utilized a modified Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 checklist. The review was conducted between September to December 2023 using Google Scholar, PubMed, and Web of Science databases. These are some of the most used databases in systematic literature review. All published articles relating to the research were eligible for consideration in this review regardless of the year of publication. To initiate the review process, Medical Subject Headings (MSH) descriptors were outlined: “fish skin”, “burn wound”, and “wound dressing”. Several synonyms were used for each component during the search. The filter, “tilapia fish skin”, was used to restrict the search process. Only those papers whose full versions were available online were considered for the review. These papers were downloaded into a special folder for subsequent review. The identified papers were scanned through to eliminate duplicates before employing the inclusion and exclusion criteria to separate the papers.

The “tilapia fish skin” is the major focus in this research because it is the material of importance that this review paper hinges on. Different fish skin biomaterials have been studied in burn wound applications, but this review is only interested in studies that used tilapia fish skin. The “burn wound” is one of the medical problems that greatly affect communities across the world. The review is interested in all the papers that have researched on the application of tilapia fish skin in burn wound application. Lastly, the review limits the search to particularly those studies that used the tilapia fish skin as a form of “wound dressing” on burn wounds, and the main findings described in the selected papers were the target of this review.

Inclusion and exclusion criteria

After analyzing the selected 65 papers that were obtained from the databases, animal experiment studies, clinical trials, and review papers on burn wound treatment that used tilapia fish skin biomaterial, or its derivatives were included in this systematic review. In total, 18 papers met the inclusion criteria for this review. On the other hand, papers on burn wound treatment that did not use tilapia fish skin biomaterial, or its derivative were not included in the study. In addition, studies that utilized tilapia fish skin biomaterial or its derivative in the treatment of wounds that are not burn wounds were also not included in the systematic review. A total of 47 papers failed the inclusion criteria and were hence excluded for this review.

Tilapia fish skin as a xenograft

The fish skin has been utilized as a xenograft/ biological dressing in several studies. The fish skin has been preferred instead of xenografts extracted from other mammalian sources like pigs, cattle, and human cadavers. These mammalian sources have been reported to pose a risk for transmitting diseases and causing autoimmune reactions. They are also contra-indicated by religious beliefs and are being expensive and in limited supply [27]. On the other hand, the fish skin has been reported to exhibit excellent biocompatibility, adherence to the wound, biodegradation, as it contains collagen type I and III which play a critical role in wound healing. It also has anti-inflammatory properties and reduces pain, providing moist environment essential for wound healing process [28–30].

Recent studies in Brazil and other countries have utilized the Nile tilapia fish in treating burn wounds. In the preliminary studies prior to using the tilapia fish skin in treating burns, it was reported that the tilapia fish skin does not harbor infectious microbiota and that it is morphologically similar to the human skin [1]. The Nile tilapia fish skin was further demonstrated to be viable after being subjected to multiple sterilization processes, including chemical sterilization, glycerolization and irradiation [31,32]. It has been shown that the derivatives of tilapia fish skin, such as gelatin powder, remain stable even after ultraviolet radiation sterilization at high doses and it does not interfere with the cross linkage of the collagen structure [33]. Besides, the collagen extracted from tilapia fish species has been said to have sufficient thermal stability. Huang et al. (2016) [34] reported that collagen from tilapia fish skin has a higher thermal stability with a better heat resistance, and its structural stability could be useful in replacing the mammalian collagen.

Researchers have further conducted some human trials on the Nile tilapia fish skin as a wound dressing for second-degree and third-degree burns. The results so far have reported that the tilapia fish skin facilitates wound healing (as shown in Fig. 2 (Left)) and greatly reduces scarring on the affected area. This is because the tilapia fish skin contains huge amounts of collagen type I which is similar in morphology to the collagen in the human skin. The tilapia fish skin also contain proline and alanine which encourage the synthesis of collagen in the wound and subsequently result in wound healing [30,31]. This suggests that combining tilapia fish skin with another robust material in wound healing would further enhance the healing process of burn wounds.

In several isolated studies conducted in Fortaleza, Brazil, which utilized the tilapia fish skin as a xenograft biomaterial (Fig. 3), the results showed that wound dressing changes were not as frequent as compared to those that use gauze as the dressing can stay for a period of 10 days, unlike gauze dressing which has to be changed daily [36]. These results were consistent with a different study that also reported fewer dressings on wounds that used tilapia skin as compared to those that used SSD as shown in Fig. 2 (Right) [35]. The wound healing process was also reported to have been enhanced due to presence of collagen nanofibers and the need for pain medication was reduced [1]. Complete re-epithelialization of the superficial partial thickness burns, with no side effects has also been observed [31,32], with wound healing without any scars or other changes in the burned areas [37]. These results are consistent with what was reported by Magnusson et al. (2017) [38] where a fish skin product derived from the North Atlantic cod (*Gadus morhua*) was used to treat acute and chronic wounds. This study concluded that the unique biomechanical properties of the fish skin graft enable it to be used in the treatment of burn wounds.

A number of animal trials have also been conducted using the tilapia fish skin with rats and donkeys as main test subjects [29,30]. One study used the Nile tilapia fish skin as a xenograft on experimental burns in rats and the results showed no changes in both the biochemical and hematological parameters [31]. In another research study, Nile tilapia fish skin was used as a biological dressing for full thickness cutaneous metacarpal wounds in donkeys. Rapid wound healing and local microbial activity inhibition were observed [30].

Use of tilapia fish skin as an acellular dressing

Acellular fish skin (AFS) is basically fish skin that has undergone tissue decellularization. AFS has been one of the recent advances in the treatment of burns using xenografts. The decellularization process involves removing the host cells that can stimulate an immune response while minimizing the structural changes of the matrix [39]. The techniques used in the decellularization process are chemical, physical, and enzymatic methods [40]. A combination of the methods has been used in different studies to reduce the negative effects of each method [41].

In one study, the tilapia acellular dermal matrix (TADM) was reported to have promoted cellular metabolic activity, differentiation, and mineralization of stem cells [42]. Fish derived acellular dermal matrix (ADM) that are rich in omega-3 polyunsaturated fatty acids have also shown promising results in studies on treating chronic diabetic foot ulcers (DFUs), necrotic angiodermatitis, calciphylaxis wounds, and iatrogenic calcinosis cutis [43]. The omega-3 fatty acids present in AFS facilitated a faster progression of the wound from inflammatory phase of wound healing. This is possible because omega-3 fatty acids can minimize inflammatory reactions on the wound and promote cytokines that aid in wound healing. Acellular fish skin matrix has also been reported to significantly decrease the wound surface area and the wound depth in patients with reported hard-to-heal wound ulcers [44].

The AFS exhibit further advantages in wound healing applications because their porous microstructure that ranges from 20 to 100 μm pore size allows easy in-growth of the dermal cells and capillaries, which simplifies cell adhesion and cell growth [45]. This porous and spongy nature of the AFS also becomes essential in the transportation of nutrients and oxygen through the membrane to the wound. In addition, a study that compared TADM and commercial porcine acellular dermal matrix revealed that, TADM had better morphology, higher thermal stability, degradation, and more suitable water vapour transmission [39].

Clinical and pre-clinical trials involving AFS has been reported to reduce the healing duration of burn wounds to 10–11 days for superficial partial thickness burns as compared to 2 weeks when using established standard treatment methods. For deep partial-thickness burns, the burn wound has been reported to heal in approximately 21 days as opposed to over 3 weeks when using known treatment methods like silver sulphadiazine 1 % cream and gauze [1,5]. Another study aimed at comparing the healing rate between fish skin acellular dermal matrix (ADM) against porcine small-intestine submucosa extracellular matrix in 81 patients with full-thickness burn wounds reported that the wounds that were treated with fish skin ADM healed significantly faster [46]. The presence of omega-3 polyunsaturated fatty acids (PUFAs) adds to the possible benefits of using fish skin acellular dressings as compared to those extracted from mammalian sources. The omega-3 PUFAs found in fish oil have shown to exhibit profound effects on the healing process of wounds [47]. It has also been reported to enhance epithelialization [48] and accelerating the closure of open wounds [49]. In their study, Alexander & Supp (2014) [47] concluded that as much as omega-3 PUFAs have beneficial effect on the epithelialization and closure of wounds, they also inhibit the deposition of collagen in the later stages of wound healing which can be attributed to minimizing the formation of scar on the healed wound.

Silver nanoparticles doped fish skin as a wound dressing material

Silver is an inert metal generally harmless to human tissues in its non-ionized form. In the presence of moisture like wound fluids and exudates, silver readily ionizes to form $Ag+$ and other biologically active ions that can bind to proteins and sulphydryl groups on the cell membrane of bacteria. The antimicrobial effect of silver arises when the silver has been absorbed into the bacteria where they act as cytoplasmic poisons [50].

Utilizing the above characteristic of silver, some studies have either loaded fish skin-based biomaterials with silver or have used

silver nanoparticles (Ag NPs) to sterilize fish skin biomaterials for wound healing applications. In one study, the researchers decorated decellularized fish skin scaffold with silver nanoparticles for wound healing applications [51]. The results indicated that, the decellularized fish skin scaffold exhibited antibacterial activity besides enhancing cell migration and proliferation due to the high content of collagen type I from the fish skin itself.

Different techniques have been used in sterilizing fish skin biomaterial before being applied on a wound to aid the healing process. It has been reported elsewhere that, application of Ag NPs presented some advantages as compared to chlorhexidine gluconate 4 % and povidone iodine 10 % in sterilizing the fish skin biomaterial based on resulting collagen fibre integrity and microbial count [52]. A concentration of 250 μg/mL Ag NPs has been reported to be ideal in fish skin sterilization for effective antimicrobial effect and reducing collagen destruction in the process [53].

Processed sponges from tilapia fish skin

As shown in Fig. 4 below, the tilapia fish skin can also be processed into collagen sponges or peptides which can have various applications. The collagen peptides derived from the Nile tilapia fish skin through composite enzymatic hydrolysis were used to treat burns in animal models, and it was reported that the process of wound healing was enhanced [9]. Significant effects on scratch closure were reported when marine collagen peptides at a concentration of 50 μg/mL were used *in vitro* scratch assay. Similarly, collagen extracted from tilapia fish has been able to be electrospun [54] and acid-solubilized [55] and then applied in wound healing applications. The results have equally shown that, the collagen is able to accelerate the healing process of the burn wound in rat models. The rapid wound healing was linked to the stimulating effect of the extracted collagen to recruit and activate macrophages so that they can produce chemotactic growth factors, aid proliferation of fibroblasts, and angiogenesis after upregulation of TGF-β1, bFGF, and α-SMA genes expression and enhanced TGF-β1 and VEGF expression [54,55].

Tilapia fish skin has also been able to be processed into collagen sponges and used in wound healing applications. When processed into collagen sponges, the biomaterials retain the inherent triple helical structure and the biological characteristics of the collagen [56]. Tilapia fish skin collagen sponge which was cross-linked by glutaraldehyde has demonstrated it was suitable for applications in wound healing. The cross-linked collagen sponge exhibits a high degree of porosity and interconnectivity which was reported to be helpful in the absorption of exudates on the wound, supply of oxygen, and cell proliferation [57]. Furthermore, the cross-linking enhances the stability and tensile strength of the collagen in the sponge. Sponges derived from tilapia fish skin have also demonstrated excellent coagulation and hemostatic abilities [58]. They can bind to specific sites on blood cells and platelets to accelerate the process of clotting. The high porosity of these sponges also necessitates absorption of blood thus effectively promoting haemostasis.

Wang [59] managed to synthesize dialyzed tilapia skin collagen sponge (DTSCS) and self-assembled tilapia skin collagen sponge (STSCS) from tilapia fish skin through freeze drying. The objective was to explore the possibility of using DTSCS and STSCS as medical dressings and compare their characterization properties. It was reported that the biomaterials are suitable for applications as homeostatic agents and wound dressings. The materials demonstrated excellent biocompatibility, porosity, high thermal stability and had no apparent rejection following their implantation.

Isolated macromolecules from the fish skin

The recent studies have mostly utilized the fish skin as a whole or decellularized in burn wound healing applications. Besides these strides, some researchers are now exploring the extraction of the molecules from the fish skin which are critical in the wound healing

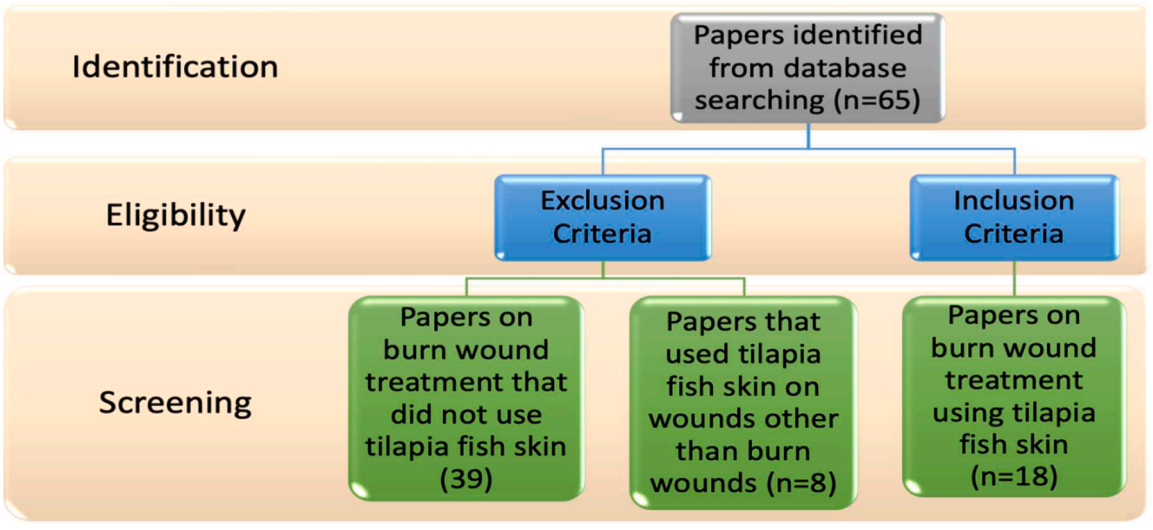

Fig. 1. The modified PRISMA flow diagram of search process.

process such that, only such molecules should be used in the healing applications unlike using the entire fish skin or simply decellularizing it.

In one study, gelatin and fucoidan were extracted from tilapia fish skin and they were mixed and reacted with tannic acid [60]. The resulting gelatin-fucose gum-tannic acid hydrogel wound dressing demonstrated excellent antibacterial, antioxidant, cytocompatibility, and haemostatic properties. This hydrogel wound dressing was reported to have fostered wound healing by promoting the expression of vascular endothelial growth factor (VEGF), platelet endothelial cell adhesion molecule-1 (CD-31), alpha-smooth muscle actin (α-SMA) and enhancing collagen deposition on the wound site [60]. It also reduced wound microbiome colonization, decrease expression of pro-inflammatory factors, and it effectively regulates the conversion of wound macrophages to M2 which is the anti-inflammatory phenotype. All these processes consequently reduce the inflammatory response thereby accelerating wound healing. Collagen has been reported to aid the recruitment and activation of macrophages so that they can produce chemotactic growth factors, aid proliferation of fibroblasts, and angiogenesis after upregulation of TGF-β1, bFGF, and α-SMA genes expression and enhanced TGF-β1 and VEGF expression [61,62].

Marine peptides have been extracted from tilapia fish skin and used in wound healing applications. Marine peptides are a product of collagen degradation and they have been reported to have good hygroscopicity and moisture retention [63]. Different studies have also demonstrated that marine peptides combined with chitosan promote skin wound healing and neovascularization [64,65]. Ouyang et al. (2018) [66] developed chitosan-marine peptides hydrogels for wound dressing applications and the results demonstrated that the hydrogels had antibacterial activity besides enhancing cell proliferation and migration (Fig. 1).

Prospective future use of tilapia fish skin biomaterial

The current studies have already demonstrated that tilapia fish skin biomaterial is biocompatible, and it contains the principal component of the extracellular matrix, collagen, which promotes the wound healing process through the deposition of freshly formed fibres and granulation tissue on the wound bed thus fostering the healing process [67]. Collagen also fosters the migration of fibroblasts onto the wound [68] and it promotes angiogenesis [69]. The advantages of using tilapia fish skin centers on enhancing the wound healing pathway other than addressing the major setback in the wound healing process which is bacterial infection on the wound site. We propose that future studies should consider processing the tilapia fish skin biomaterial into collagen-based hydrogels [66] that can be used as wound dressings for burn. In so doing, the wound dressing will retain the advantages that the tilapia fish skin has while making the dressing being able to provide moist environment for wound healing [14].

These hydrogel dressings can further be designed to incorporate antimicrobial agents like silver/SSD or bacteriophages. This will enable the hydrogel dressings to be a complete treatment modality for burn wounds since they will be able to fight bacterial infections on the wound site while providing the conducive environments for the regeneration and epithelialization of the skin tissue on the wound site. The use of silver/SSD have already been proved to be effective in treating burn wounds [5,6]. On the other hand, the use of bacteriophages in the treatment of burn wounds is a novel research area, with some studies reporting the efficacy of phage therapy in the treatment of burn wounds [70,71]. The other reason why researchers are turning their attention to phages in the treatment of burn wounds is because phages have proved to be bactericidal even against those bacteria that have demonstrated to be antibiotic-resistant [71]. Bacterial infection is a major challenge in burn wound treatment, hence incorporating antibacterial agents will greatly enhance the effectiveness of the dressing.

Besides demonstrating promise in the wound healing applications, there is still need for further studies to be conducted on the suitability of using tilapia fish skin biomaterial in treating deeper burn wounds. In addition, there is need for experimental studies to be done to standardize the processing and characterization techniques of the tilapia fish skin biomaterial so as to effectively translate the biomaterial into a product that can be commercialized. However, the limitations of using tilapia fish skin biomaterial should clearly be

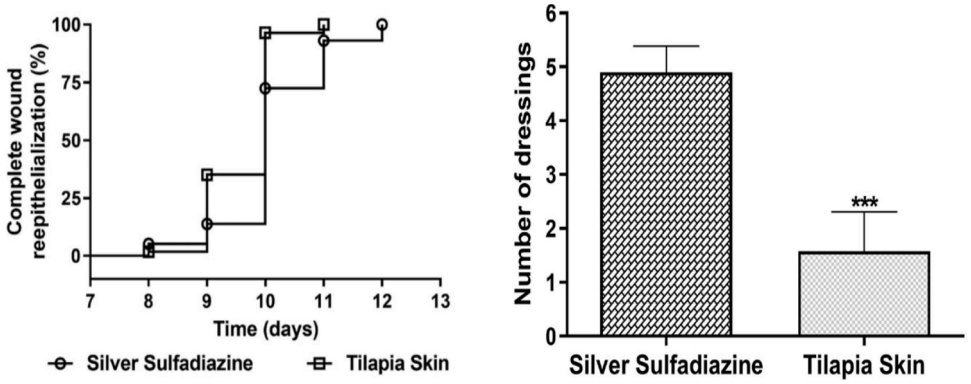

Fig. 2. (Left) A graph of time (in days) against complete wound reepithelialization in patients when using SSD vs tilapia fish skin. For each treatment day (*horizontal line*), the probability of reepithelialization completion up to that day is indicated (*vertical line*). **(Right)** A graph showing the number of wound dressings performed on patients that were treated with SSD vs tilapia fish skin. Unpaired *t*-test was used for comparison (***$p < 0.001$). The data represented correspond to the mean and standard deviation of the values obtained [35].

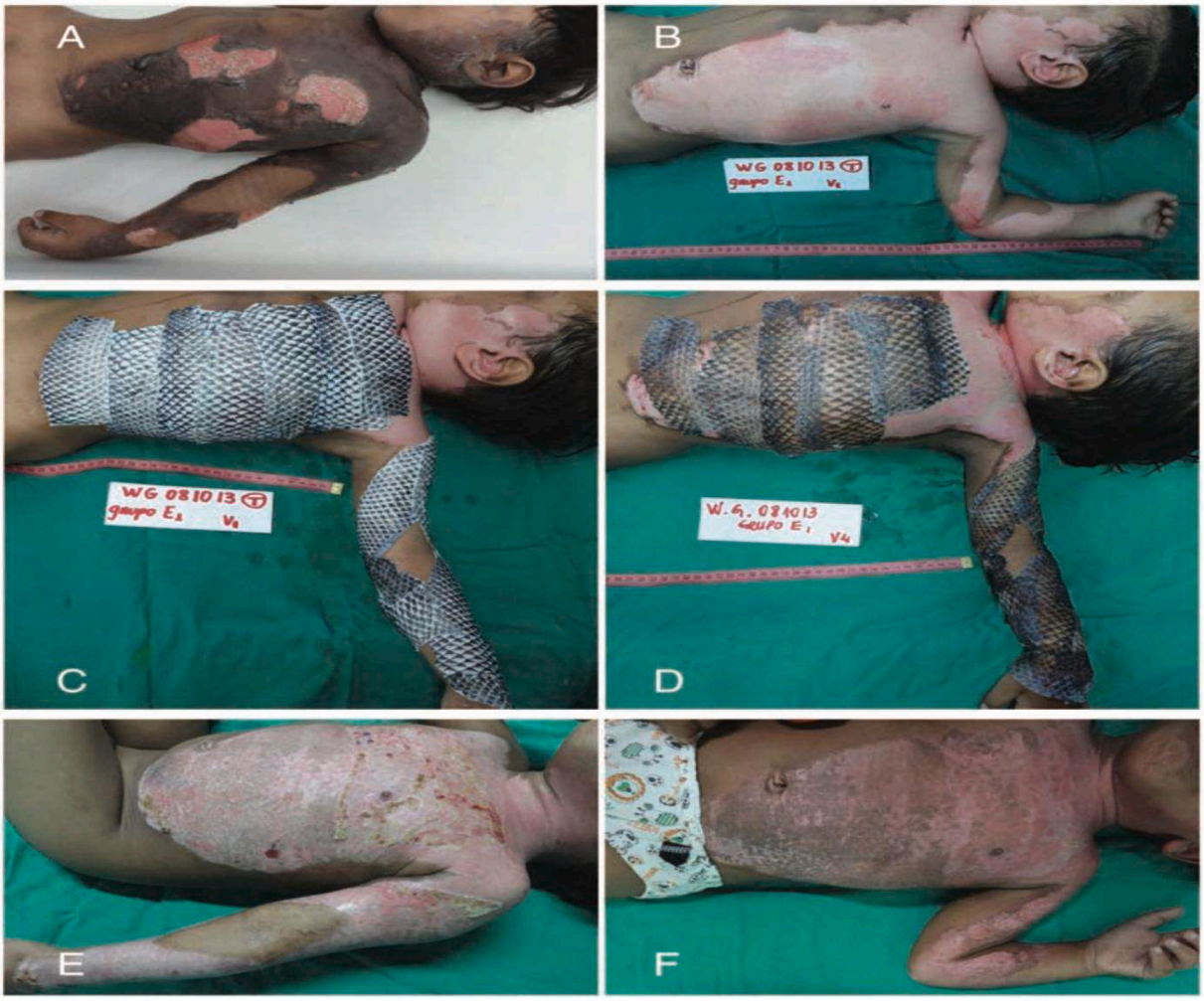

Fig. 3. A 3 year old boy with burn scalds (**A**); The necrotic skin tissue and blisters were removed to allow effective adherence between the tilapia fish skin biomaterial and the wound bed (**B**); Tilapia fish skin biomaterial application to the burn wound (**C**); Appearance of the wound showing good adherence of the tilapia fish skin biomaterial six days after its application (**D**); Tilapia fish skin biomaterial removed after 10 days with complete re-epithelialization of the skin tissue (**E**); Post-treatment assessment of wound appearance a week after removing the tilapia fish skin biomaterial dressing (**F**) [36].

researched and addressed before developing a commercial product.

Conclusion

According to current research, it is evident that tilapia fish skin biomaterial plays an important role in burn wound treatment applications. The numerous advantages of the tilapia fish skin have been reported when used singularly or in combination with other materials like silver nanoparticles. This review has summarized how the tilapia fish skin has played several roles as wound dressing biomaterial that enhances the wound healing process. The tilapia fish skin can be peeled off from the fish and used as a xenograft biological dressing, or it can be decellularized to form AFS, dopped with other materials like silver nanoparticles to enhance their antimicrobial effects or processed into collagen peptides. The tilapia fish skin has also been found to have the macromolecules that are essential in wound healing when extracted from it and used in wound healing applications. The collagen extracted from the tilapia fish skin can be synthesized into hydrogels which can be used as wound dressings. Further to that, recent studies are utilizing these hydrogels to load bacteriophages in them to treat bacterial infections in wound healing applications. Table 1 above provides a summary highlighting the key findings of this review paper. These findings clearly demonstrates the potential that the tilapia fish skin biomaterial has in wound healing applications.

Even though the evidence is promising, the difference in the healing duration between the tilapia fish skin biomaterial and the existing treatment using silver sulphadiazine is not satisfactory. Furthermore, the risk of infection developing on the wound during healing has not entirely been addressed. This justifies why the use of tilapia fish skin biomaterial is yet to be a universally accepted

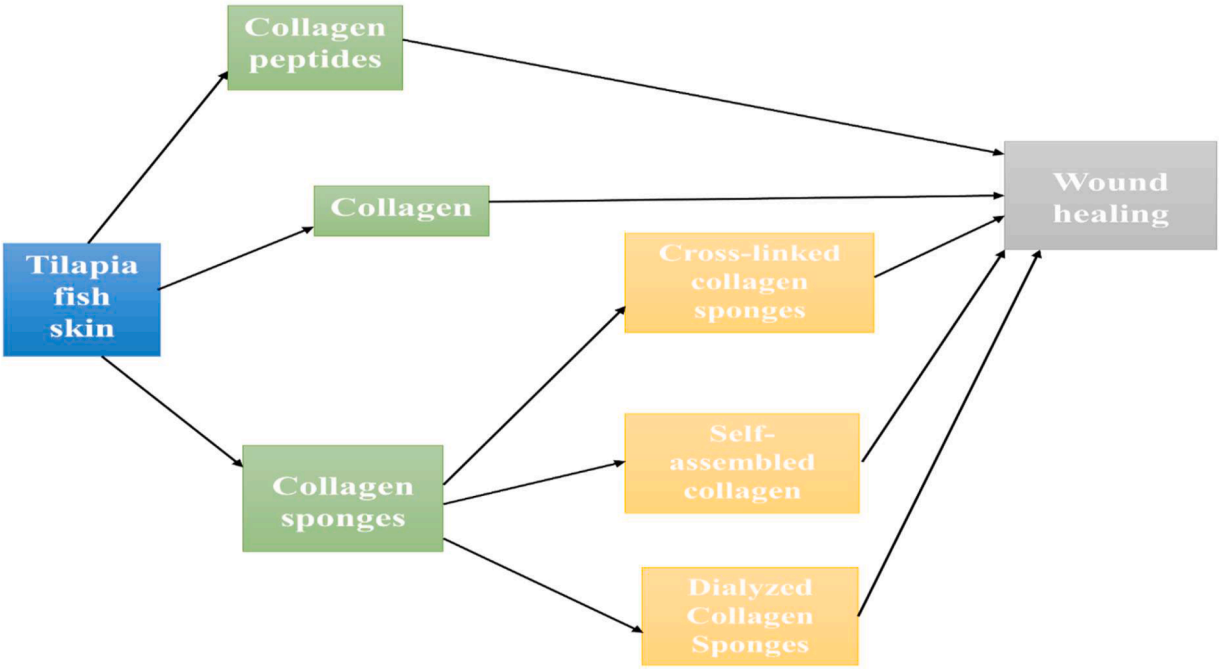

Fig. 4. Selected processing pathways of tilapia fish skin for wound healing applications.

Table 1
Key findings for different tilapia fish skin biomaterials.

Tilapia fish skin biomaterial	Key attributes
Xenograft	Excellent biocompatibility [28–30]. Adherence to the wound [35]. Biodegradation [28–30]. Provides a moist environment [28–30]. Contain proline and alanine which encourage the synthesis of collagen on the wound [30,31].
AFS	Greatly reduces scarring [47]. Promotes cellular metabolic activity, differentiation, and mineralization of stem cells [42]. The omega-3 fatty acids present in AFS facilitate a faster progression from inflammatory phase of wound healing [43]. significantly decrease the wound surface area and the wound depth [44]. They have a porous microstructure that allows easy in-growth of the dermal cells and capillaries, which simplifies cell adhesion and cell growth [45].
Dopped with Silver Nanoparticles	Silver nanoparticles enhance the antimicrobial effect [50,51]. Enhances cell migration and proliferation due to the high content of collagen type I [51]. sterilizing the fish skin biomaterial with Ag reduces collagen destruction as compared to using other chemicals [53].
Processed Sponges/Peptides	Ability to enhance wound closure hence accelerating the healing process [54,55]. Ability to recruit and activate macrophages so that they can produce chemotactic growth factors, aid proliferation of fibroblasts, and angiogenesis [54,55]. Retains the inherent triple helical structure and the biological characteristics of collagen [56]. Cross-linked collagen sponge exhibits a high degree of porosity and interconnectivity which has been reported to be helpful in the absorption of exudates on the wound, supply of oxygen, and cell proliferation [57]. Demonstrates excellent coagulation and homeostatic abilities [58]. Excellent biocompatibility, porosity, and high thermal stability [59].
Isolated Macromolecules	Demonstrates excellent antibacterial, antioxidant, cytocompatibility, and haemostatic properties [60]. Fosters wound healing by promoting the expression of VEGF, CD-31, α-SMA and enhancing collagen deposition on the wound site [60]. Reduces wound microbiome colonization, decrease expression of pro-inflammatory factors, and it effectively regulates the conversion of wound macrophages to M2 which is the anti-inflammatory phenotype [61,62]. Exhibit good hygroscopicity and moisture retention [63].

treatment protocol for burn wound healing. Therefore, this gives room for future studies which should aim at greatly reducing the treatment duration as well as eradicating the risk of infection on the wound bed during wound healing. The tilapia fish skin biomaterial must be processed together with other robust materials and therapies to attain a synergistic effect. Future studies should explore extracting essential macromolecules from tilapia fish skin that are critical in the re-epithelialization and inhibiting bacterial growth on the wound site. The extracted macromolecules can then be combined with other biomaterials or bacteriophages to enhance the

synergistic effect on overall wound healing. The combination should be tailored to ensure faster wound healing and prevention of post healing complications like hypertrophic scarring which can alter the functions of the affected site.

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Declaration of competing interest

The authors declare 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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