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ISSN 1462 2815

TILAPIA FISH SKIN IN MEDICINE: A COMPREHENSIVE REVIEW OF ITS THERAPEUTIC POTENTIAL

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Abstract

Tilapia fish skin, a readily available and sustainable resource, has emerged as a promising material in various medical applications, particularly in wound healing and neovaginoplasty. This comprehensive review explores the unique properties of tilapia fish skin and its potential therapeutic applications. In the treatment of burns, studies have shown that tilapia fish skin grafts exhibit comparable efficacy to conventional methods such as silver sulfadiazine cream, with benefits including faster wound healing, reduced dressing changes, and decreased analgesic requirements. Moreover, tilapia fish skin demonstrates antibacterial, antiviral, anti-inflammatory, and analgesic effects, making it suitable for long-term treatments, especially in war-torn or resource-limited regions. In neovaginoplasty procedures, tilapia fish skin serves as a cost-effective scaffold, enabling surgery to be performed via exclusive vaginal access without the need for laparoscopy or laparotomy. Studies have reported favourable outcomes, including the formation of neoepithelium resembling normal vaginal mucosa and the absence of post-operative complications. Additionally, tilapia fish skin has shown promise in promoting cellular proliferation and tissue regeneration, particularly in tendon repair. Its decellularized form has been found to enhance cellular functions and accelerate wound healing. Overall, the therapeutic implications of tilapia fish skin are vast, ranging from wound healing to oral conditions like extraction wounds and bone necrosis. However, further large-scale studies are warranted to establish its widespread and official use in clinical settings. Nevertheless, tilapia fish skin stands as an excellent, economical xenograft with the potential to revolutionize medical treatments, particularly in underserved communities globally.

ISSN 1462 2815

INTRODUCTION

One of the major components of connective tissue is collagen. Today approximately 28 subtypes of collagen have been discovered (1). Of the subtypes, collagen type 1 is commonly found in the body as a part of bone, dentin, cartilage as well as plays a part in cell building (2). The molecular weight of collagen is 300 kDa, diameter is approximately 14-15 Å, and has length of 2800 Å approximately. It has a triple helical formation due to 3 polypeptide alpha chains with a repeating sequence of Gly-X-Y) n with Pro often located at positions X and Y (3). Collagen is the most prolific protein found in vertebrates, accounting for approximately 25-30% of animal protein (4). Collagen has high water absorption capacity, is biocompatible, had low immunogenicity and biodegradability, is highly porous, has an innate ability to combine with other materials and has almost no religious or ethical constraints on being used. Due to all of these advantages, it makes collagen a key for use in the food, cosmetics, biomedical and pharmaceutical industries. Many studies have been conducted in which type 1 collagen was used, but the sources were predominantly gotten from mammalian sources such as calf and pig. Thus, there was a risk of transmission of animal origin diseases such as mad cow disease, hand-foot-mouth disease, Creutzfeld- Jacob disease (5). Religious constraints also prevent the use of bovine and porcine origin products. Recently, collagen derived from marine animals specifically fish collagen has gained immense popularity in the cosmetic and health industry due to the lowered risk of transmission of zoonotic infections and comparatively lowered immunogenicity (6).

The main component of human dentin and bone is hydroxyapatite and type I collagen, which is very similar to that in fish skin and scales. Tilapia is the common name for fish belonging the tilapine cichlid tribe. Type I collagen derives from Nile Tilapia scientifically Oreochromis niloticas has been found to show a higher T (d) (37°C). This is very close in T (d) to mammalian collagens, and thus had been proposed optimistically for use in biomedical application (7-9).This comprehensive review delves into the emerging role of tilapia fish skin, a readily available and sustainable resource, in various medical applications. We explore the unique properties of tilapia fish skin and its potential in wound healing, tissue regeneration, and drug delivery.

Table 1: Tilapia Fish Skin in Wound Healing

Author	Year	Study Type	Test performed	Results
Lima Júnior EM, Moraes Filho MO, Forte AJ, et al. (10)	2019	Randomized controlled trial	Superficial partial thickness burns admitted less than 72 hours from thermal burns treated with tilapia skin grafts (acellular fish skin graft) or with conventional silver sulfadiazine cream.	Burn wounds with tilapia skin graft healed at same rate as silver sulfadiazine cream.
Lima-Junior EM, de Moraes Filho MO, Costa BA et al. (11)	2019	Case report	A 23-year-old man, without any preexisting health conditions, sustained burns of both superficial partial thickness and deep thickness, for which he received treatment involving the application of tilapia fish skin.	Re-epithelization on days 12 and 17 with no dressing changes and no side effects.
Costa BA, Lima Júnior EM, de	2019	Case report	A 3-year-old boy suffering from superficial partial thickness burns underwent	Re-epithelization was seen on day 10 with good adherence of

Moraes Filho MO et al. (12)			treatment involving the application of tilapia fish skin.	skin to wound bed with no side effects.
Lima Júnior EM, De Moraes Filho MO, Costa BA, et al. (13)	2020	Randomized controlled trial	Glycerolized tilapia skin grafts or conventional silver sulfadiazine cream were used to treat both superficial and deep partial thickness burns.	Burn wounds treated with tilapia skin grafts healed faster. They had less analgesic requirements and required fewer dressing changes.
Lima Júnior EM, de Moraes Filho MO, Costa BA, et al. (14)	2021	Randomized controlled trial	Superficial partial thickness burns were managed in an outpatient setting using either glycerolized tilapia skin grafts or conventional silver sulfadiazine cream.	Burn wounds treated with tilapia skin grafts healed faster. They were less painful and more cost-effective.
Lima Júnior EM, de Moraes Filho MO, Costa BA, et al. (15)	2021	Randomized comparision study	Glycerolized tilapia skin along with silver-impregnated sodium carboxymethylcellulose dressing were utilized in the treatment of superficial partial thickness burns.	The intake of analgesics and the level of pain experienced were comparable for both tilapia skin and silver-impregnated sodium carboxymethylcellulose dressing, with no observed side effects. However, glycerolized tilapia skin was deemed superior for burn management.
Putri NM, Kreshanti P et al. (16)	2022	Case series	Four patients with full thickness burns on both sides of their limbs received treatment involving either tilapia skin or paraffin-impregnated gauze.	Limbs treated with tilapia fish skin required fewer dressing changes compared to the alternative treatment. Additionally, no adverse effects were observed in either treatment group.
Liu et al. (17)	2022	Prospective cohort	-	TP2-5 and TP2-6 use showed favourable results in cellular proliferation when treated with HaCaT keratinocytes. Pro-angiogenic properties were displayed with enhancement of human umbilical vein endothelial cell migration and neovascularization promotion.
Liu et al. (18)	2022	Retrospective cohort	Decellularized tilapia fish skin that has been manufactured and cross-linked with EDC (1-ethyl-3-(3-dimethylaminopropyl) carbodiimide) and NHS (N-hydroxysuccinimide).	Cross-linked decellularized tilapia fish skin showed enhanced functions. It showed an enhanced cellular proliferation which included the induction of movement and differentiation of tendon-derived stem cells.

In a Phase II pilot study conducted in Brazil, wound healing in 30 pediatric patients with superficial partial thickness burns, admitted within 72 hours of thermal injury, was compared between those treated with glycerolized tilapia skin and conventional silver sulfadiazine cream. While tilapia fish skin demonstrated strong adherence to the wound bed, resulting in reduced dressing changes and anesthesia requirements post-treatment, no significant differences were observed in the duration of complete wound healing, total analgesic consumption during treatment, or pain experienced during treatment between the groups treated with fish skin and silver sulfadiazine cream (10).

In a Brazilian case report, tilapia fish skin was employed in the treatment of a 23-year-old man with no comorbidities who had sustained superficial partial thickness burns on his right upper limb and deep partial thickness burns on his left upper limb due to a gunpowder explosion. Following the application of tilapia skin, the patient required dressing changes, experienced no adverse effects, and exhibited wound re-epithelialization on days 12 and 17 of treatment (11).

In a case report from Brazil, tilapia skin was utilized in the treatment of a 3-year-old pediatric patient with superficial partial thickness burns affecting the left side of the face, neck, anterior thorax, abdomen, and left arm, which accounted for approximately 18% of the body surface area. The tilapia skin demonstrated good adherence to the wound bed, and no adverse effects were observed. Complete re-epithelialization was achieved by day 10 of treatment. (12).

In a Phase II randomized controlled trial conducted in Brazil, wound healing outcomes were compared in 62 patients with superficial and deep partial thickness burns treated either with glycerolized tilapia skin grafts or conventional silver sulfadiazine cream. The results indicated that burn wounds treated with tilapia skin exhibited superior healing, requiring fewer dressing changes and resulting in reduced analgesic requirements compared to those treated with silver sulfadiazine cream. (13).

A phase III randomized control trial in Brazil compared wound healing in 115 outpatients with superficial partial thickness burns that were treated with glycerolized tilapia skin grafts or with conventional silver sulfadiazine cream. Burn wounds treated with tilapia skin grafts had faster wound epithelialization rates with fewer dressing changes. They had lesser analgesic requirements, decreased visual analog scale, burns specific pain anxiety scale, and electronic von Frey measurements. Treatment with fish skin reduced the treatment cost by 42.1% per patient (14).

Table 2: Tilapia Fish Skin as a Graft for Neovaginoplasty

Author	Year	Patients	Results
Dias MTPM et al. (20)	2019	A female patient diagnosed with Mayer-Rokitansky-Küster-Hauser syndrome presenting with primary amenorrhea.	No post-operative complications.
			Neovaginal length after 180 days – 8-9cm
			Neoepithelium - stratified squamous epithelium with five cell layers, ectasic blood vessels, and occasional desquamated epithelial cells.
			Tilapia skin graft was partially absorbed.
Dias MTPM et al. (21)	2019	A female patient experiencing complete occlusion of the vaginal canal following radiotherapy treatment for vaginal cancer.	No post-operative complications.
			Neovaginal lengths immediately after surgery –10 cm
			Neovaginal lengths after 60 days – 7cm
			Neoepithelium – no vaginal strictures or granulation tissue.
			Tilapia skin graft was partially absorbed.
Dias MTPM et al. (22)	2020	Three female patients diagnosed with Mayer-Rokitansky-Küster-Hauser syndrome presenting with primary amenorrhea and normal secondary sexual characteristics.	No post-operative complications.
			Neovaginal lengths immediately after surgery – 9-10 cm
			Neovaginal lengths after 180 days – greater than 6cm
			Neoepithelium – stratified squamous, high expression of cytokeratin and fibroblast growth factor (FGF) and a weak expression of epidermal growth factor receptor (EGFR).
			Tilapia skin graft was partially absorbed.
Rodríguez ÁH et al. (23)	2020	29-year-old male patient for male- female gender reaffirming surgery	No post-operative complications.
			Neovaginal length after 3 weeks – 16 cm
			Tilapia skin graft was completely reabsorbed.
	2020		No post-operative complications.

Slongo H et al. (24)		Single patient male-female gender reaffirming surgery	Neoepithelium – resembled vaginal mucosa
			Neovaginal length after 60 days – 8 cm
Torres ATS et al. (25)	2022	11 female patients with Mayer-Rokitansky-Küster-Hauser syndrome	No post-operative complications.
			Neoepithelium – stratified squamous epithelium with increased FGF and EGFR
Teófilo CR et al. (26)	2023	Cross-sectional study with 7 cisgender women with Mayer-Rokitansky-Küster-Hauser syndrome who had previously undergone neovagina reconstruction using Nile tilapia fish skin.	Neo-epithelium – squamous cells without atypia
			Mean vaginal length after 1 year follow-up – 8.3cm

A randomized comparison study compared wound healing in superficial partial thickness burns were treated with glycerolized tilapia skin and silver-impregnated sodium carboxymethylcellulose dressing. Burn wounds analgesic intake and pain was similar for both tilapia skin and silver-impregnated sodium carboxymethylcellulose dressing with no side effects. Glycerolized tilapia skin was superior for burn management (15). A case series in Indonesia compared wound healing after full thickness burns on both sides of the limb treated by tilapia skin or paraffin-impregnated gauze. Fewer dressing changes were required with treatment with tilapia skin as compared paraffin-impregnated gauze. Adverse effects were not seen in either treatment (16).

A prospective cohort study in Taiwan compared use of synthetic peptides from tilapia skin (TP2, TP2-5, TP2-6) for wound healing. TP2-5 and TP2-6 use showed favourable results in cellular proliferation when treated with HaCaT keratinocytes. Pro-angiogenic properties were displayed with enhancement of human umbilical vein endothelial cell migration and neovascularization promotion. In a murine model topical treatment of wounds with TP2-5 and TP2-6 healed significantly faster (17). A retrospective cohort in China showed that cross-lined decellularized tilapia skin had an improved function and enhanced cellular proliferation. This thus underlined the efficacy of tilapia cross-lined decellularized skin graft in treatment of tendon repair (18).

A study by Dias MTPM et al. used tilapia fish skin graft for neovaginoplasty in one female patient with Mayer-Rokitansky-Küster-Hauser syndrome with primary amenorrhea. No post-operative complications were seen. At the 10-day follow-up the neovaginal length was between 8-9cm. The neoepithelium was stratified squamous epithelium five cell layers thick, with the presence of ectasic blood vessels, and occasional desquamated epithelial cells. Tilapia skin graft was partially absorbed (20).

A study by Dias MTPM et al. used tilapia fish skin graft for neovaginoplasty in a female patient with total occlusion of the vaginal canal after radiotherapy for vaginal cancer. Neovaginal length immediately after surgery was 10 cm. Neovaginal length after 60 days was measured to be 7cm. No vaginal strictures or granulation tissue was seen in the neoepithelium. Tilapia skin graft was partially absorbed (21).

A study by Dias MTPM et al. used tilapia fish skin graft for neovaginoplasty in three female patients with Mayer-Rokitansky-Küster-Hauser syndrome with primary amenorrhea and normal secondary sex characters. No post-operative complications were seen and immediate neovaginal length after surgery was 9-10cm. At 180 days followup the neovaginal lengths was greater than 6 cm. Further immunological and histological analysis showed that the neoepithelium was both macro and microscopically is not distinguishable from normal vaginal epithelium. Protein markers

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are also similar. The neoepithelium was stratified squamous epithelium with a high expression of cytokeratin and FGF and a lower expression of EGFR similar to a normal vaginal epithelium. Tilapia skin graft was partially absorbed (22).

A male- female gender reaffirming surgery study by Rodríguez ÁH et al. used tilapia fish skin graft for neovaginoplasty. No post-operative complications were seen. The neovaginal length after 3 weeks was 16 cm. Tilapia skin was completely reabsorbed into neovaginal mucosa (23).

A male- female gender reaffirming surgery study by Slongo H et al. used tilapia fish skin graft for neovaginoplasty. No post-operative complications were seen. The neovaginal length after 60 days was 8 cm. The neoepithelium resembled normal vaginal mucosa (24).

A case series by Torres ATS et al. used tilapia fish skin graft for neovaginoplasty in eleven female patients with Mayer-Rokitansky-Küster-Hauser syndrome. No post-operative complications were seen, and the neoepithelium – stratified squamous epithelium with increased FGF and EGFR similar to normal vaginal mucosa (25).

A study by Teófilo CR et al. was a cross-sectional study with 7 cisgender women with Mayer-Rokitansky-Küster-Hauser syndrome who had previously undergone neovagina reconstruction using Nile tilapia fish skin. It studied the clinical, cytological and vaginal microbiota. Neo-epithelium was squamous cells without atypia. The mean vaginal length after 1 year follow-up was maintained at 8.3cm. Vaginal contents showed an intermediate microbiota (Nugent score of 4) and hormonal results were found to be compatible with menacme with no colposcopic changed seen (26).

DISCUSSION

With the advancement of science, the treatment of wound healing after burns has evolved. Recently, the use of Nile tilapia fish skin has shown promising results as compared to traditionally used methods. In treatment of burns, dressing changes form an important component of successful wound healing. Fewer dressing changes were seen with the use of tilapia fish skin along with a good adherence to wound bed. The total analgesic requirement in the entire treatment was also reduced. The economic burden of treatment was also reduced with the treatment of tilapia fish skin as compared to conventional methods. This could be beneficial as a treatment option in war-ridden and third world countries that are hurting for proper resources (16). In addition to burns, the use of tilapia skin can be expanded to explosive injuries as they have a long storage life and can be easily stored at room temperature. Wounds treated with fish skin do not require recurrent repairs thus making them an ideal for battlefield wound treatment. Furthermore, they have antibacterial, antiviral, anti-inflammatory and analgesic effect on wounds this benefiting long term treatments (19). Some human tissues have a relatively slower rate of regeneration, such as tendon tissue. Regeneration of tendon tissue is usually carried out by mammalian-derived scaffolds. Liu and colleagues however showed that the same could be achieved with decellularized tilapia fish skin (18).

In neovaginoplasty, use of Nile tilapia fish skin as a scaffold is advantageous as surgery can be performed as a one-step procedure without laparoscopy or laparotomy through exclusive vaginal access. This is thus more economical than the traditional methods. A risk of shrinkage if the scaffold and a long term regular compliant dilation are few of the disadvantages for which long term follow-up is essential (22). A cross-

ISSN 1462 2815

sectional study was carried out by Teófilo CR et al. on 7 cisgender women with Mayer-Rokitansky-Küster-Hauser syndrome who had previously undergone neovagina reconstruction using Nile tilapia fish skin.

After 1 year follow-up the mean vaginal length was found to be 8.3 cm with a similar microbiota and neoepithelium as that seen in normal vaginal mucosa (26). Thus, this study shows that there needs to more such trials all around the world before the official use of this tilapia skin scaffold can be used. Even in cases of vaginal canal recontruction after radiotherapy for vaginal cancer tilapia fish skin acts as a true scaffold without side-effects and good anatomical and functional reports noted.

As a scaffold it acts allows metaplasia and epithelialization of scar tissue thus forming histologically similar epithelium as that of normal vagina. Thus Nile tilapia fish skin has a great potential to be used as a scaffold for vaginal reconstruction as it is economical, wide availability, ease of application and high effectiveness. Disadvantages are the regular dilation for which long term follow-ups are needed (21).

Secondary healing with scar formation is seen as a by-product in certain procedures such as wound healing of post-surgical site, healing of biopsy site in oral submucous fibrosis, in inflammatory bowel diseases like Chron's disease or ulcerative colitis. The secondary healing shows following characteristics such as fibrosis, reduced vascularity, infiltration of inflammatory cells and keratinization of the epithelium.

The healing by tilapia fish skin is seen to combat the secondary healing characteristics such as wound healing by angiogenesis, inflammatory cell disappearance, epithelial cell proliferation and re-epithelialization by keratinocytes. Thus, healing by tilapia fish skin avoids fibrosis and shows faster healing. Thus, Nile tilapia fish skin as a scaffold or graft can also be used to treat other oral conditions such as healing of extraction wounds, healing of dry socket, bone necrosis, grafting, flap surgeries and many more (27). Thus, this is shows the immense therapeutic implications and potential uses for tilapia fish skin which is currently a major research lacunae.

CONCLUSION

Nile tilapia fish skin as a xenograft has immense potential for use in the treatment of burns as well as a scaffold for neovaginoplasty. The use of tilapia fish skin has shown promising results by increased rates of healing, fewer dressing changes and reduced analgesic requirements after treatment as well as being more economical, in treatment of burns. The use in neovaginoplasty has shown promise by making the surgical procedure easy and cost-effective as compared to more traditional methods.

There is are many other therapeutic application of the tilapia skin graft as in the treatment of extraction wounds, healing of dry socket, bone necrosis, grafting, flap surgeries, wound healing of post-surgical site, healing of biopsy site in oral submucous fibrosis, in inflammatory bowel diseases like Chron's disease or ulcerative colitis for which further research must be carried out. Thus Nile tilapia fish skin graft can be used as an excellent , economical xenograft for delivering cost-effective treatments especially in war-ridden and third world countries. However, more large-scale, world - wide studies must be carried out before the widespread and official use can be established.

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