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## Nile tilapia skin in the treatment of second-degree burns: a systematic review with meta-analysis

### **Pele de tilápia do Nilo no tratamento de queimaduras de segundo grau: revisão sistemática com meta-análise**

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### ABSTRACT

**Objective:** Systematically review the effects of using Nile tilapia skin (NTFS) for management/treatment in patients with second-degree skin burns, when compared with two treatments containing silver, hydrofiber dressing or sulfadiazine cream (AgSD). **Methodology:** Systematic review with meta-analysis performed in January 2023, using PubMed, Web of Science, CINAHL, Scopus, Cochrane and Gale databases, to identify relevant randomized clinical trials. **Results:** In total, five randomized trials were identified comparing the use of NTFS with two types of silver-based treatment of second-degree skin burns. Occlusive dressings with NTFS significantly reduced pain levels, measured using the Visual Analogue Scale - VAS ( $p=0.0008$ ), time (measured in days) for complete wound healing, corresponding to re-epithelialization of 95% or more of the initial burn ( $p=0.002$ ), and the number of dressings needed until complete healing of the burn ( $p=0.0004$ ). **Conclusion:** The results confirm the positive effects of using the NTFS dressing on patients with second-degree burns and can benefit public health systems, especially in developing and resource-poor countries.

**Keywords:** Wound healing; Dressing changes; Nile tilapia skin; Silver-impregnated sodium carboxymethylcellulose; Silver sulfadiazine cream

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### RESUMO

**Objetivo:** Revisar sistematicamente os efeitos do uso da pele de tilápia do Nilo (NTFS) para manejo/tratamento em pacientes com queimaduras cutâneas de segundo grau, quando comparado com dois tratamentos contendo prata, curativo de hidrofibra ou creme de sulfadiazina (AgSD). **Metodologia:** Revisão sistemática com meta-análise realizada em janeiro de 2023, utilizando as bases de dados PubMed, Web of Science, CINAHL, Scopus, Cochrane e Gale, para identificar ensaios clínicos randomizados relevantes. **Resultados:** No total, foram identificados cinco ensaios randomizados comparando o uso de NTFS com dois tipos de tratamento à base de prata para queimaduras cutâneas de segundo grau. Os curativos oclusivos com NTFS reduziram significativamente os níveis de dor, mensurados pela Escala Visual Analógica - VAS ( $p=0,0008$ ), tempo (medido em dias) para cicatrização completa da ferida, correspondendo à reepitelização de 95% ou mais da queimadura inicial ( $p=0,002$ ) e o número de curativos necessários até a cicatrização completa da queimadura ( $p=0,0004$ ). **Conclusão:** Os resultados confirmam os efeitos positivos do uso do curativo NTFS em pacientes com queimaduras de segundo grau e pode beneficiar os sistemas de saúde pública, especialmente em países em desenvolvimento e com poucos recursos. **Resumo no segundo idioma (português ou espanhol), com as mesmas regras e a mesma formatação do anterior.**

**Palavras-chave:** Cicatrização de feridas; Mudanças de curativos; Pele de tilápia do Nilo; Carboximetilcelulose sódica impregnada de prata; Creme de sulfadiazina de prata

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## INTRODUÇÃO

Globally, burns are the fourth most frequent type of injury, after traffic accidents, falls, and physical violence. Regardless of the factors that cause burns, they are complicated wounds, difficult to heal and associated with high mortality rates (MARKIEWICZ-GOSPODAREK et al., 2022).

Second-degree injuries affect both the epidermis and the dermis, generating the appearance of vesicles or blisters, in addition to pain and local erythema, and can be divided into superficial and deep lesions. The superficial lesions, addressed in this study, and also called superficial partial-thickness burns, which, although painful, have a healing time of around 14 to 21 days (AZULAY; AZULAY, 2017).

Silver-impregnated dressings or sulfadiazine cream (AgSD) are among the current standard therapies for burn care (MAY et al., 2022). However, occlusive dressings, such as using Nile tilapia (*Oreochromis niloticus*) skin (NTFS), have demonstrated beneficial effects in humans (adult and child patients) (LIMA JÚNIOR et al., 2020a; MIRANDA; BRANDT, 2019). This species ranks fourth in the world as the most cultivated, according to the Food and Agriculture Organization of the United Nations (FAO) and its skin is a widely available and low cost by-product (BARROSO; MUÑOZ; CAI, 2019).

The objective of this systematic review was to increase the level of evidence of the effects of using Nile tilapia skin when treating patients with second-degree burns compared to treatment with a silver-based dressing or cream on: pain; time for complete healing of the wound (re-epithelialization); and number of dressing changes.

## METHODOLOGY

This is a systematic review that was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (PAGE et al., 2021). The method design was guided by the Cochrane Collaboration Handbook (HIGGINS et al., 2019a). Thus, the guiding question was defined: Is there a difference between the use of Nile tilapia skin and silver-impregnated carboxymethylcellulose dressing or silver sulfadiazine cream in pain relief during dressing change, time to complete wound healing (reepithelialization) and number of dressings in patients with second degree burns?

The searches in the databases occurred in January 2023. Six data sources were used: National Library of Medicine (MEDLINE-PubMed), Web of Science, Science Direct, Scientific Electronic Library Online (Scielo), Elsevier SciVerse Scopus (SCOPUS) and Cochrane Library.

To perform the search in the databases, the following keywords were used: tilapia AND skin AND burns, accepted as Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH). Searches were restricted to trials with human participants, with full texts

published in English, Spanish, or Portuguese. For the construction of the guiding question, the PICO strategy was used (P - Population; I - Intervention; C – Control and comparison; O - Outcome) (Table 1)

The results retrieved in the search process were exported and stored on the Rayyan QCRI platform (<https://www.rayyan.ai>) to be classified. Duplicates were electronically removed and titles and abstracts were screened to remove irrelevant articles. Full-text copies of studies that met the inclusion criteria were assessed against predefined eligibility criteria independently by two reviewers and any disagreements were resolved by a third reviewer. Inclusion and exclusion criteria are described in Table 1.

Data were extracted by two reviewers independently using standardized forms. The form included the following information: study characteristics (author name, country, and year of publication), participants (sample size, age, and sex), intervention characteristics (including dose and study duration), and primary and secondary outcomes (Table 2).

The methodological quality of the included studies was assessed by two reviewers (author 1 and author 2), independently and blinded by the first and second reviewers. It followed the risk of bias guidelines of the Cochrane Handbook Risk of Bias Approach (HIGGINS et al., 2019a). Any discrepancies were resolved by consensus and a third reviewer was consulted when necessary.

For the analysis of the inverse of variance, the means and standard deviation of the results of each study were used to compare the data found. Heterogeneity was calculated using the Q2 and I2 test and significance was set at  $p < 0.10$  or  $I^2 > 50\%$ . The value of  $p < 0.05$  was adopted as statistically significant. The meta-analytic models were described in forest-plots. All analyses were performed using Review Manager 5.4. (HIGGINS et al., 2019b).

## RESULTS

A total of 556 records from these electronic databases were identified in the initial search. After removing duplicates, 514 articles were selected by title and abstract. Of these, 509 were excluded for various reasons. Fifteen full-text articles were retrieved and assessed for eligibility. Of the 15 potentially relevant articles, 10 were excluded and 5 studies were finally included in the qualitative synthesis and meta-analysis (LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b; MIRANDA; BRANDT, 2019). The literature screening process and results are described in Figure 1. The main characteristics of the included studies, as well as primary and secondary outcomes, are summarized in Table 2.

Five RCTs, involving 218 patients (188 adults and 30 children), were included and divided between experimental (n=110) and control (n=108) groups. Nile tilapia skins were subjected to two decontamination and sterilization processes to ensure the safety of their use in humans: chemically sterilized, glycerolized, and irradiated (LIMA JÚNIOR et al., 2020a,

2021a; MIRANDA; BRANDT, 2019); or chemically sterilized (LIMA JÚNIOR et al., 2020b, 2021b). Control groups were divided into two subgroups: two studies treated with carboxymethylcellulose containing 1.2% silver (Aquacel AG® - ConvaTec, Brazil) (LIMA JÚNIOR et al., 2021a; MIRANDA; BRANDT, 2019) and three with silver sulfadiazine cream 1.0% (LIMA JÚNIOR et al., 2020a, 2020b, 2021b). These articles were all published between 2019 and 2021, one in a Brazilian journal and four in American journals, one was published in Portuguese (MIRANDA; BRANDT, 2019) and four in English (LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b), and all studies were carried out in Brazil. One study involved pediatric patients (LIMA JÚNIOR et al., 2020b), and the other studies were in adult populations (LIMA JÚNIOR et al., 2020a, 2021a, 2021b; MIRANDA; BRANDT, 2019).

**Table 1** – Inclusion and exclusion criteria

Criteria	Inclusion	Exclusion
Study selection	RCTs	Retrospective and prospective comparative observational studies, systematic reviews, conference abstracts, case series, case reports, narrative reviews, editorials, opinions; basic research, case control studies, semi-random control studies, cohort studies, studies performed in animals; repeat published studies; contained incomplete data
Population	Adults or children with second-degree burns	Full thickness burns
Geographical location	Publications from any country	None
Language	English, spanish or portuguese	Other than english, spanish, or portuguese
Interventions	Use of Nile tilapia skin (NTFS)	Other treatments that do not use NTFS
Comparisons	Silver-impregnated sodium carboxymethylcellulose dressings or silver sulfadiazine cream	Other treatments that do not use silver-impregnated sodium carboxymethylcellulose dressings or silver sulfadiazine cream
Outcomes of interest	Pain during dressing change, time for complete wound healing (re-epithelialization), and number of dressings	Did not include at least one primary endpoint

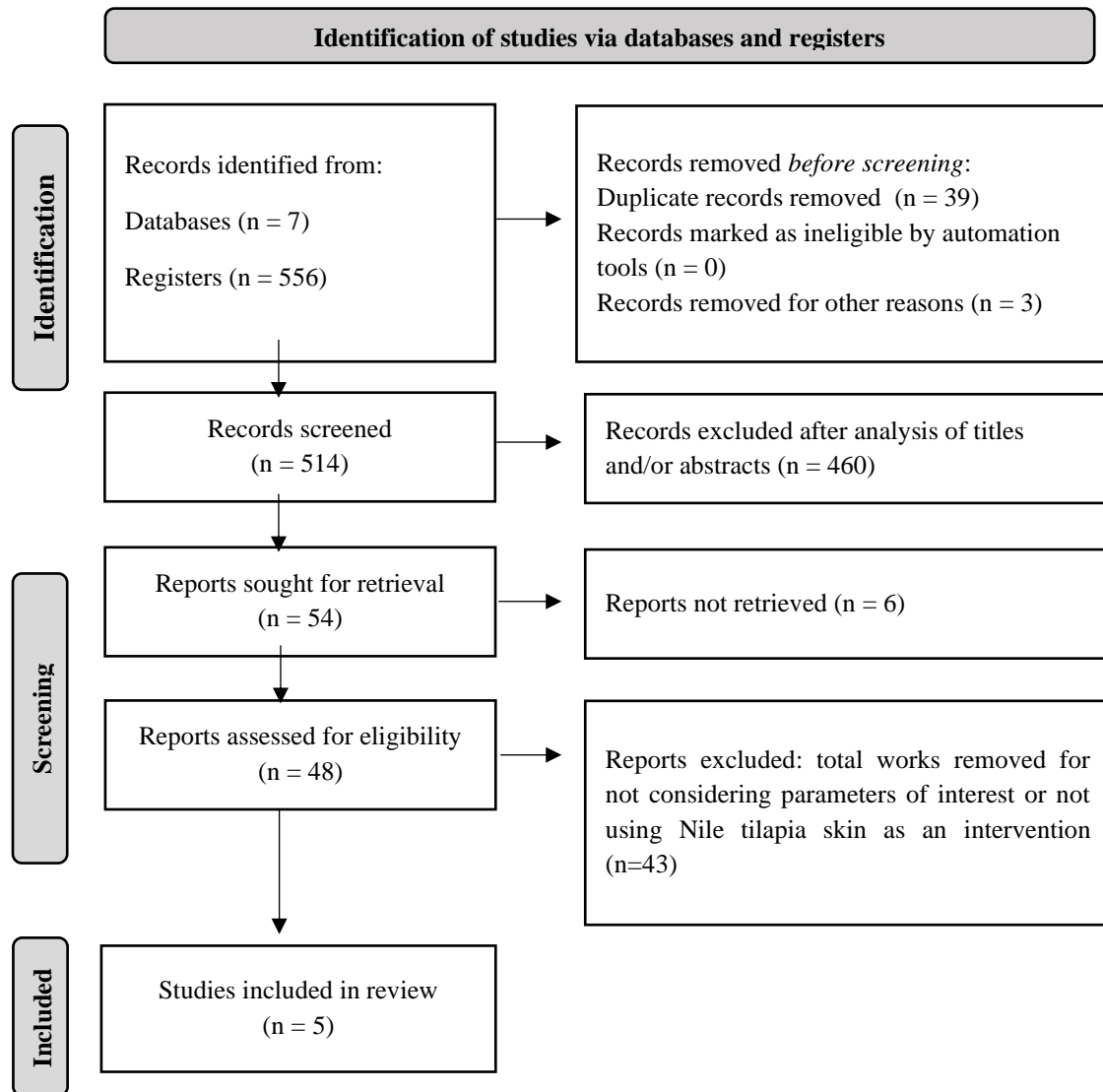
Abbreviations: RCT, randomized controlled trial; NTFS, Nile tilapia skin. Source: Authors (2023)

### Results of primary outcomes

The selected works, defined as primary parameters, studied the effect of using NTFS on pain levels (measured through the VAS)(LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b), time for complete wound healing (corresponding to re-epithelialization of 95% or more of the initial burn) (LIMA JÚNIOR et al., 2020a, 2020b, 2021a; MIRANDA; BRANDT, 2019), and

number of dressings replaced at any time during treatment in patients with second-degree burns (LIMA JÚNIOR et al., 2020a, 2021a, 2021b; MIRANDA; BRANDT, 2019).

**Figura 1** – PRISMA flowchart of the study selection process



Source: Authors (2023)

Data extracted from primary studies were meta-analyzed for pain levels measured by VAS in the group of patients treated with occlusive biological dressing with Nile tilapia skin and showed significant improvement ( $p=0.008$ ) when compared to treatment with carboxymethylcellulose containing 1.2% silver and also when compared to treatment with silver sulfadiazine cream ( $p=0.02$ ), as control groups. The total effect test showed that treatment with Nile tilapia skin was significantly better than the combined effects of treatments composed of carboxymethylcellulose containing 1.2% silver and silver sulfadiazine cream ( $p=0.001$ ) (Figure 2).

**Table 2 - Characteristics of the studies included in the meta-analysis**

Author/ Country/Year	Control	Intervention	Number of participants	Characteristics of the participants	Parameters analyzed <sup>1</sup>
MIRANDA AND BRANDT / Brazil / 2019	Carboxymethylcellulose containing 1.2% silver	Nile tilapia skin	Control = 15 Intervention = 15	30 adults (20 to 60 years) Hospitalized with burns of up to 10% of the body surface	<b>Number of days for wound healing.</b>
LIMA JUNIOR et al. / Brazil / 2020a	1% silver sulfadiazine cream	Nile tilapia skin	Control = 10 Intervention = 9	19 adults ( $\geq 18$ and $< 50$ years) Hospitalized with burns involving 10% to 20% of the body surface	<b>Pain, number of days for wound healing, number of dressing replacements, use of dipyrrone.</b>
LIMA JUNIOR et al. / Brazil / 2020b	1% silver sulfadiazine cream	Nile tilapia skin	Control = 15 Intervention = 15	30 children (2 to 12 years) Hospitalized with burns greater than 20% of the body surface	<b>Pain, number of days for wound healing, number of dressing replacements, use of dipyrrone, pain [Revised Faces Scale (FPS-R)].</b>
LIMA JUNIOR et al. / Brazil / 2021a	Carboxymethylcellulose containing 1.2% silver	Nile tilapia skin	Control = 12 Intervention = 12	24 adults ( $\geq 18$ and $\leq 70$ years) Hospitalized with burns of up to 10% of the body surface	<b>Pain, number of dressing replacements, use of dipyrrone, anxiety-related pain, pain (von Frey test); workload reduction.</b>
LIMA JUNIOR et al. / Brazil / 2021b	1% silver sulfadiazine cream	Nile tilapia skin	Control = 58 Intervention = 57	115 adults (18 to 70 years) Hospitalized with burns of up to 10% of the body surface	<b>Pain, number of days for wound healing, number of dressing replacements, use of dipyrrone, anxiety-related pain, pain (von Frey test), economic cost.</b>

<sup>1</sup>Primary parameters are described in bold; Source: Authors (2023)

The results of the primary parameters of pain levels measured using the VAS (LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b), time (days) for complete wound healing (corresponding to re-epithelialization of 95% or more of the initial burn) (LIMA JÚNIOR et al., 2020a, 2020b, 2021a; MIRANDA; BRANDT, 2019) and number of dressings replaced at any time during treatment (LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b) were expressed clearly, in such a way that they enabled safe extraction of the values to be meta-analyzed.

Data extracted from primary studies were meta-analyzed for pain levels measured by VAS in the group of patients treated with occlusive biological dressing with Nile tilapia skin and showed significant improvement ( $p=0.008$ ) when compared to treatment with carboxymethylcellulose containing 1.2% silver and also when compared to treatment with silver sulfadiazine cream ( $p=0.02$ ), as control groups (Figure 2).

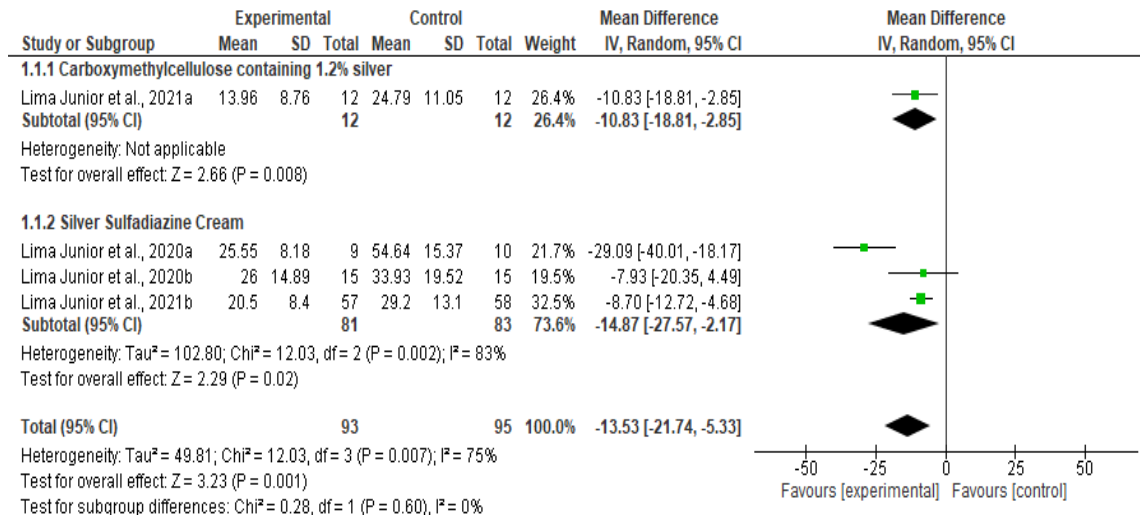
The total effect test showed that treatment with Nile tilapia skin was significantly better than the combined effects of treatments composed of carboxymethylcellulose containing 1.2% silver and silver sulfadiazine cream ( $p=0.001$ ) (Figure 2).

The result of the meta-analysis of the number of days for wound healing (corresponding to 95% or more re-epithelialization of the initial burn) demonstrated that treatment with Nile tilapia skin reduces time, but this difference was not significant ( $p=0.08$ ) in relation to the group treated with a dressing composed of carboxymethylcellulose containing 1.2% silver. When compared with treatment with 1% silver sulfadiazine cream, the results revealed a significant difference ( $p<0.00001$ ). The global effect test showed a significant difference when the treatment with Nile tilapia skin was compared with the combined treatments with a dressing composed of carboxymethylcellulose containing 1.2% silver and 1% silver sulfadiazine cream ( $p=0.0001$ ) (Figure 3).

The result of the meta-analysis revealed a decrease in the number of dressings used during the treatment of burns in the group of patients treated with occlusive biological dressing with Nile tilapia skin, but this difference was not significant when the patients were treated with carboxymethylcellulose containing 1.2% silver ( $p=0.16$ ). When compared with treatment with silver sulfadiazine cream, the results showed a significant difference ( $p=0.03$ ). The global effect test showed a significant difference when the treatment with Nile tilapia skin was compared with the combined treatments

with a dressing composed of carboxymethylcellulose containing 1.2% silver and 1% silver sulfadiazine cream (p=0.0004) (Figure 4).

**Figure 2 - Forest Plot** comparing the data extracted from the included studies on the assessment of pain levels measured using the Visual Analogue Scale (VAS) of patients treated with Nile tilapia skin dressing and treated with carboxymethylcellulose containing 1.2% of silver or silver sulfadiazine cream



Source: Authors (2023)

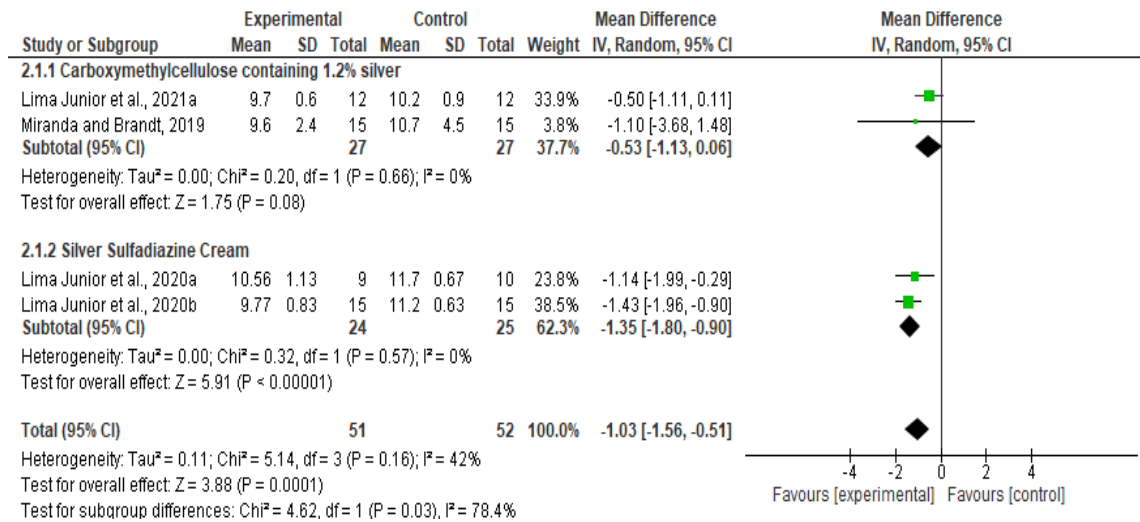
### Results of secondary outcomes

Only one study reported the analysis of the anxiety-related pain parameter (BSPAS) and one reported a significant decrease (p=0.035) with the use of NTFS (LIMA JÚNIOR et al., 2021b), while in the other, no difference was observed between the treatment with occlusive dressing with NTFS and silver-based dressing (p=0.3100) (LIMA JÚNIOR et al., 2021a).

Pain levels measured by the electronic von Frey test were collected by two studies and one reported a significant reduction (p=0.003) with the use of NTFS (LIMA JÚNIOR et al., 2021b). However, no significant difference was observed (p=0.4886) in the other study (LIMA JÚNIOR et al., 2021a).

The amount of dipyron (in milligrams) required for patient analgesia throughout the burn treatment was significantly lower (p<0.001) in the NTFS group compared to the silver sulfadiazine cream group (LIMA JÚNIOR et al., 2021b). However, another three studies measured this parameter and the results did not reveal a significant difference (p>0.05) in the amount (mg) of dipyron consumed for analgesia (LIMA JÚNIOR et al., 2020a, 2020b, 2021a).

**Figure 3 - Forest Plot** comparing the results (mean and standard deviation) of the number of days for wound healing (corresponding to re-epithelialization of 95% or more of the initial burn) of patients treated with Nile tilapia skin and treated with carboxymethylcellulose containing silver 1.2% or silver sulfadiazine cream

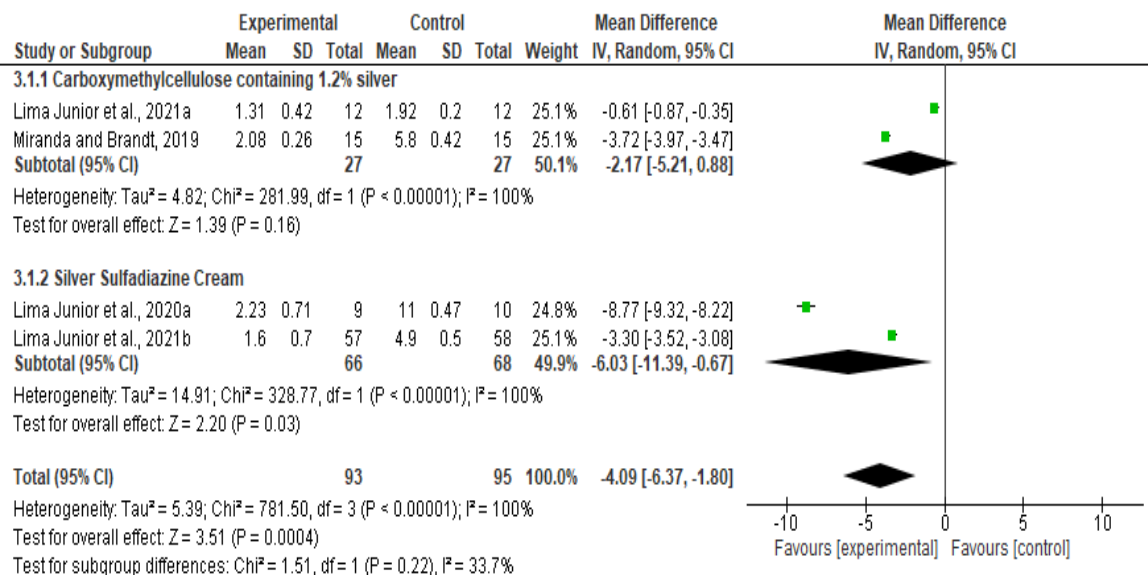


Source: Authors (2023)

In the group of patients in which NTFS treatment was used for second-degree burns, the results showed a reduction in pain, measured by the Faces Pain Scale - Revised (FPS-R), there was no difference between treatments (p=0.1020)(LIMA JÚNIOR et al., 2020b).

In the cost-benefit analysis, the results showed that the total cost of dressing for the 57 patients treated using NTFS was US\$613, with an average cost of US\$11 ± US\$1 per patient. In contrast, the total cost of dressing for the 58 patients treated with silver sulfadiazine cream was US\$1,123, with a mean cost of US\$19 ± US\$1 per patient. Therefore, expenditure was significantly higher in the control group, with silver sulfadiazine cream (p<0.001), and the use of NTFS resulted in a 42.1% reduction in the mean cost of treatment per patient. When compared to the control group, the experimental group also showed an approximately 50.0 percent reduction in mean costs for every 1 percent of total body surface area (\$4 for Nile tilapia skin versus \$8 for cream of silver sulfadiazine) and for each day of treatment (\$1 for NTFS versus \$2 for silver sulfadiazine cream) (LIMA JÚNIOR et al., 2021b).

**Figure 4 - Forest Plot** comparing the data extracted from the number of times it was necessary to replace the occlusive biological dressing with Nile tilapia skin and treatment with carboxymethylcellulose containing 1.2% silver or silver sulfadiazine cream



Source: Authors (2023)

When analyzing the risk of bias of the included studies, all studies (100%) were described as “random sequence generation”, "allocation concealment" and "selective reporting" (LIMA JÚNIOR et al., 2020a, 2020b, 2021b; MIRANDA; BRANDT, 2019). Three studies (60%) were assessed as high risk of bias, as they reported that it was not possible to blind participants and staff, as well as the evaluation of results (LIMA JÚNIOR et al., 2021a, 2021b; MIRANDA; BRANDT, 2019). The other two studies (40%) had an uncertain risk of bias because they did not report whether the shielding of participants and personnel and evaluation of results was effective (LIMA JÚNIOR et al., 2020a, 2020b). On the topic of incomplete outcomes, all studies had an uncertain risk of bias, as they have insufficient reports of losses and exclusions to allow judgment. All other biases were uncertain, justified by insufficient information to assess whether an important risk of bias exists. The risk of bias in the RCTs determined using the Cochrane Collaboration Tool is summarized in Figure 5.

**Figure 5 - Risk of bias assessment for RCTs**

	Random sequence generation	Allocation concealment	Selective reporting	Blinding (participants and personnel)	Blinding (outcome assessment)	Incomplete outcome data	Other sources of bias
Lima Junior et al., 2020a	+	+	+	?	?	?	?
Lima Junior et al., 2020b	+	+	+	?	?	?	?
Lima Junior et al., 2021a	+	+	+	-	-	?	?
Lima Junior et al., 2021b	+	+	+	-	-	?	?
Miranda and Brandt, 2019	+	+	+	-	-	?	?

Source: Authors (2023)

## DISCUSSION

The search for drugs and supplies that optimize healing at more affordable costs has increased over time. New healing therapeutic technologies from alternative sources are already known, such as those of plant (phytotherapics); physical (laser therapy and ozone therapy); and biological origin (skin therapies) (PINA; ROCHA, 2021). Treatments for burned patients are expensive, and require a lot of time from health professionals and for rehabilitation (MIRANDA, 2018). However, despite the large number of studies related to treatment options for superficial and partial thickness burns, the optimal treatment protocol has not yet been established (PIPELZADEH et al., 2022). More recently, cell-based therapies have been designed, which can lead to further improvements in clinical outcomes (ABDEL-SAYED et al., 2019) but, these modern approaches are unrealistic for everyday clinical practice in under-resourced public health systems in developing countries (LIMA JÚNIOR et al., 2021a).

The ideal dressing for skin lesions is one that is preferably low-cost, easy to obtain, easy to handle, malleable, resistant to traction, painless, maintains moisture, avoids bacterial contamination, and, mainly, favors the process of epithelialization and angiogenesis (LIMA JÚNIOR et al., 2021a, 2021b; MIRANDA; BRANDT, 2019; NOGUEIRA et al., 2022). Before considering NTFS as a therapeutic option for burns in

humans, preclinical studies were performed and demonstrated a non-infectious microbiota (LIMA JUNIOR et al., 2016), a morphological structure similar to human skin (ALVES et al., 2015, 2018), and good results when used for the treatment of experimental burns in animal models (LIMA-JUNIOR et al., 2017). Clinical studies using NTFS for the treatment of burn wounds have also shown beneficial effects and appear to represent an alternative to conventional treatments, but the results are still controversial (LIMA-JUNIOR et al., 2017; LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b; MIRANDA; BRANDT, 2019; PINA; ROCHA, 2021).

### Primary parameters

In this systematic review with meta-analysis of the data of the primary parameters included, we demonstrated that the use of NTFS, as an occlusive biological dressing, was able to reduce the pain of patients with second-degree burns, measured by the VAS, when compared to treatments using a dressing composed of carboxymethylcellulose containing 1.2% silver or silver sulfadiazine cream. The pain reported shortly after the burn is due to direct stimulation and damage to nociceptors present in the epidermis and dermis, which leads to the transmission of nerve impulses by C and A-delta fibers to the dorsal horn of the spinal cord (CASTRO; LEAL; SAKATA, 2013). The magnitude of the impulse is modulated by peripheral stimuli and descending influences from the brain (CÁCERES-JEREZ et al., 2018; CASTRO; LEAL; SAKATA, 2013). The decrease in pain in the treatment of patients with NTFS may be due at the first moment to attenuation of the loss of fluids and proteins and through the nerve covering, allowing the patient to resume activities without disturbing the healing process (ABDEL-SAYED et al., 2019).

Although the pain associated with the burn can be considered as part of the mechanisms of tissue protection and regeneration, prolonged acute pain can lead to pain centralization, increased incidence of persistent pain, development of depression or post-traumatic stress disorder (RETROUVEY; SHAHROKHI, 2015), and decreased trust in the medical team, negatively affecting the outcome of wound care and decreasing adherence to rehabilitation therapies (RICHARDSON; MUSTARD, 2009). The significant decrease in pain indicates occlusive biological treatment with NTFS as a promising treatment, as pain relief is a basic human right, thus, being not only a clinical, but also an ethical issue that involves health professionals (MARTINEZ; GRASSI; MARQUES, 2011).

The articles included in this review considered that the lesion was repaired when the re-epithelialized area corresponded to 95% or more of the initial burn (LIMA JÚNIOR et al., 2020a, 2020b, 2021a; MIRANDA; BRANDT, 2019). The results of this study revealed a reduction in the number of days for complete healing of the burn in the group of patients treated with NTFS as an occlusive biological dressing, but this reduction was significant only when compared to treatment with silver sulfadiazine cream. Due to the promising results, new studies should be carried out in order to increase the level of evidence and thus elucidate the beneficial effect in relation to the treatment with carboxymethylcellulose dressing containing 1.2% silver. In fact, the biological dressing can induce faster healing, thus minimizing scar formation, while for intermediate zones it can help reduce edema and risks of thrombosis in the capillaries (ABDEL-SAYED et al., 2019).

It is possible that this beneficial result is due to the existence of a mild or moderate mononuclear inflammatory phenotype in wounds covered by this biological tissue, compared to the control groups (in which acute inflammatory reactions were evidenced), which positively influenced the time of re-epithelialization in patients treated with NTFS (LIMA-JUNIOR et al., 2017). In an animal model, with rats, NTFS collagen nanofibers were found to increase the speed of wound healing in the skin, promoting benefits in cell adhesion, proliferation, and differentiation (ZHOU et al., 2016). In this same animal species, the results showed that tilapia collagen significantly induced the expression of epidermal growth factor and fibroblast growth factor, which can promote the proliferation and differentiation of fibroblasts and keratinocytes (CHEN et al., 2019). In rabbits, using marine collagen peptides (MCPs) from Nile tilapia skin, the results also showed beneficial effects on re-epithelialization time (HU et al., 2017). In donkeys, dressing with Nile tilapia skin has been shown to accelerate the healing process, suggesting its reliable and promising application in metacarpal wounds (IBRAHIM et al., 2020).

Dressing changes require a process of cleaning the area, causing not only pain, but also delay in the healing process (MIRANDA, 2018). NTFS has been shown to exert a buffer effect, and a protective effect on the wound, providing a physical barrier that can reduce the risk of infection (ABDEL-SAYED et al., 2019). This reduction in the risk of infection is probably due to the antimicrobial activity of piscidins 3 and 4 (TP3 and TP4, respectively), antimicrobial peptides recently isolated from the skin of the fish *Oreochromis niloticus* (LAYCOCK et al., 2013). In addition, these peptides have also

been shown to beneficially modulate immune and inflammatory responses (RETROUVEY; SHAHROKHI, 2015).

It was observed that the acute inflammatory reactions were attenuated in the wound bed and directed to the dressing, which is likely due to the abundance of collagen type I (COL-1) that was degraded by the inflammatory action (KOTANIEMI et al., 2003). Despite inflammatory infiltrates, the NTFS collagen was not completely damaged, with the superficial layers being maintained, which ensured the permanence of the occlusive dressing until complete healing of the patient's skin (LIMA JÚNIOR et al., 2020a), as it was only changed when the skin was not well adhered to the wound bed (LIMA JÚNIOR et al., 2020a, 2021a, 2021b). The skin of this species has a higher composition of type I collagen and its microscopic characteristics are similar to the morphological structure of human skin, presenting a dermis composed of compact, long, and organized collagen bundles. The results of the studies did not show variations in its histological or clinical characteristics after chemical sterilization, lyophilization, and/or irradiation (LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b; MIRANDA; BRANDT, 2019).

In addition, as previously mentioned, NTFS collagen can significantly induced the expression of epidermal growth factor and fibroblast growth factor, promoting the proliferation and differentiation of fibroblasts and keratinocytes (CHEN et al., 2019), allowing good adhesion to the wound bed (MAGALHÃES; RAMIRES; ZUPPA, 2020) and the consequent reduction in dressing changes, or even remaining until complete wound healing, time spent by professionals performing dressing changes, and the amount of unpleasant sensations and physical stress felt by the patient (LIMA JÚNIOR et al., 2020a).

### Secondary Parameters

Two studies measured anxiety-related pain scores using the Burns Specific Pain Anxiety Scale (BSPAS) (LIMA JÚNIOR et al., 2021b). In one of the studies the results revealed a beneficial effect of NTFS (LIMA JÚNIOR et al., 2021b) and in the other the results revealed no difference between treatments (LIMA JÚNIOR et al., 2021a). The beneficial response of NTFS may be due to the protective effect of Nile tilapia skin on the wound, mitigating acute inflammatory reactions and reducing the number of dressing changes, as well as anxiety-related pain. In addition, it may also be related to the acceleration of the patient's recovery and adaptation process, reducing the high levels of anguish and anxiety associated with burns (HULBERT-WILLIAMS et al.,

2008). Despite pain representing an important initial protective function, as it alerts the person to the existence of a potential or real danger of external or internal origin (ECHEVARRIA-GUANILO et al., 2011), burn patients experience pain anxiety before painful procedures, including dressings (FALLAH et al., 2019; WANG et al., 2022) and can result in metabolic and immunological disorders and interfere with your recovery process (NAJAFI GHEZELJEH; MOHADES ARDEBILI; RAFII, 2017). However, further studies should be carried out, as the results are conflicting in the two studies included in this systematic review.

Two studies evaluated pain by the electronic Von Frey (LIMA JÚNIOR et al., 2021a, 2021b). While in one of the studies the results showed a benefit of the use of NTFS when compared to the results of the control group (LIMA JÚNIOR et al., 2021b), in the other study the results showed no difference between treatments (LIMA JÚNIOR et al., 2021a). In previous studies, electronic von Frey measurements revealed satisfactory reproducibility when applied to healthy areas in humans (TENA et al., 2012) and a very good positive correlation with the VAS results in burn patients (DIÓGENES et al., 2020). However, the results are contradictory and further studies should be encouraged to increase the level of evidence.

To assess the amount (in mg) of dipyron consumed, the participants received a packet with the medication and were instructed to only take it if they felt pain, respecting the prescription, and recording the amount taken on a daily control card (LIMA JÚNIOR et al., 2020a, 2020b, 2021a, 2021b). In one of the studies, the results showed a decrease in dipyron consumption when patients were treated with NTFS (LIMA JÚNIOR et al., 2021b), while the other studies did not show this difference (LIMA JÚNIOR et al., 2020a, 2020b, 2021a). Hospitalized patients with superficial and deep partial thickness burns showed a positive correlation between pain score measured on the VAS and anesthetic/analgesic needs (LIMA JÚNIOR et al., 2020a, 2021b). However, no statistically significant differences were observed for VAS pain scores and analgesic intake among outpatients with superficial partial-thickness burns treated with NTFS or silver sulfadiazine cream, likely due to the small sample size (LIMA JÚNIOR et al., 2021b).

In the group of patients in which NTFS treatment was used for second-degree burns, the results did not reveal pain reduction, as measured by the Faces Pain Scale - Revised (FPS-R) (LIMA JÚNIOR et al., 2020b). Although tilapia skin, as a biological alternative for a xenograft, appears to represent a possibility to reduce pain and the need

for dressing changes (ELMASRY et al., 2016), some methods to measure pain did not show this beneficial result, which may be due to the reduced number of studies.

Due to its good adherence to the wound bed, NTFS treatment decreases the number of dressing changes, as well as leading to faster re-epithelialization, demonstrating the reduction in the overall workload of health professionals in burn units (LIMA JÚNIOR et al., 2021b). In addition, when compared to the silver-based dressing (silver sulfadiazine cream), NTFS demonstrated a 42.1% reduction in the mean cost of treatment per patient (US\$11 versus US\$19), which may benefit the under-resourced public health systems of many developing countries, where 90% of all burns occur (GREENHALGH, 2019). The average cost of treatment per patient obtained for NTFS is also significantly less than the \$20 reported in the literature for Aquacel (ConvaTec, Bridgewater Township, N.J.), another commonly used silver-impregnated dressing (CARUSO et al., 2006). Furthermore, the use of NTFS leads to an average expense of US\$4 for every 1% of total body surface area (AUSTIN et al., 2015).

### **Risk of bias assessment**

In this systematic review, five studies that met the inclusion criteria were included. The methodological quality of individual studies was assessed based on the modified collaborative approach to meta-analysis and review of study data checklists (MACLEOD et al., 2015) and risk of bias assessment tools and other methodological criteria of published studies (KRAUTH; WOODRUFF; BERO, 2013). This analysis showed that some studies raise concerns about the lack of blinding and that blinding is not possible due to the need to observe the types of dressing for application, evaluation, replacement, and adequate removal (LIMA JÚNIOR et al., 2021b). In addition, the studies do not cite conflicts of interest, however, this can arise whenever there is a set of circumstances that creates the risk of an actual, perceived, or potential conflict of interest.

### **Strengths and limitations**

The strengths of this systematic review relate to the broad literature search strategy used to identify the evidence available to answer the research question. This is the first systematic review with a meta-analysis that systematically evaluates studies in patients with second-degree burns, in which NTFS was used versus treatment with silver-based dressings. In addition, the development and reasoning of this review was based on the

inclusion of studies evaluated through rigorous methodological quality tools. However, systematic reviews are subject to certain drawbacks and methodological limitations that must be recognized in light of the findings.

Some parameters for the evaluation of the effectiveness of the use of NTFS in the treatment of patients with second-degree burns, versus treatment with carboxymethylcellulose containing 1.2% silver dressing and silver sulfadiazine cream 1% were not meta-analyzed due to the data presentation format or due to the reduced number of studies that evaluated the same parameter, which made the quantitative analysis unfeasible (JUYBARI et al., 2020).

### **Implications and future research**

This study demonstrated beneficial effects: lower levels of pain (measured by the VAS scale), shorter time for wound re-epithelialization, and a lower number of dressings, in the treatment of second-degree burns with NTFS, as a biocompatible occlusive dressing, in children and adults, when compared to conventional treatment with silver-based dressings. None of the studies reported any sign of antigenicity, toxicity, or side effects in patients.

As Nile tilapia is the fourth most produced fish in the world, according to the Food and Agriculture Organization of the United Nations (FAO) and its skin is a waste by-product, with only 1% being used (LIMA JÚNIOR et al., 2020a; MIRANDA; BRANDT, 2019), the observed beneficial results from the use of this biological dressing encourage its use as a dermal substitute in daily clinical practice in health systems, especially in countries that have few resources (LIMA JÚNIOR et al., 2021a). However, further clinical studies are needed to increase the level of evidence.

### **CONCLUSIONS**

The results of this systematic review with meta-analysis showed that the use of Nile tilapia skin as an occlusive biological dressing attenuates pain levels, decreases the time for complete wound healing, as well as the number of dressings needed during the treatment period of the second-degree burn, in children and adults, when compared to conventional silver sulfadiazine cream 1% or carboxymethylcellulose containing 1.2% silver dressing. Given the small number of studies, this meta-analysis suggests that further studies using the skin of this species of fish be carried out in order to increase the level of evidence for this intervention.

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