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LARVOTHERAPY IN THE TREATMENT OF DIFFICULT-TO-HEAL LESIONS: INTEGRATIVE REVIEW

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ABSTRACT

Objective: To analyze the evidence available in the literature about the use of larvotherapy in the treatment of difficult-to-heal wounds. **Method:** This is an integrative review, having as a guiding question: what evidence is available in the literature about the use of larvotherapy in the treatment of wounds that are difficult to heal? The inclusion criteria were: original articles, literature review and experience reports, from 2016 to 2021, available online in full, in Portuguese, English and Spanish and that answered the research question. Exclusion criteria were: duplicate articles, letters to the editor, dissertations, theses, monographies and research with animals. Searches took place at Virtual Health Library and United Station National Library of Medicine between August and September 2021. **Results:** Ten articles were selected. The main advantages were: selective debridement, bactericidal or bacteriostatic action, and promotion of granulation tissue and healing factors. The main disadvantages were: pain, discomfort, prejudice, and weaknesses with the larval production market. **Conclusion:** The advantages found outweigh the disadvantages evidenced. Therefore, larvotherapy is favorable to treat wounds that are difficult to heal.

DESCRIPTORS: Larva. Wounds and injuries. Therapeutics. Enterostomal therapy.

LARVOTERAPIA NO TRATAMENTO DE LESÕES DE DIFÍCIL CICATRIZAÇÃO: REVISÃO INTEGRATIVA

RESUMO

Objetivo: Analisar as evidências disponíveis na literatura acerca da utilização da larvoterapia no tratamento de feridas de difícil cicatrização. **Método:** Trata-se de revisão integrativa, tendo como questão norteadora: quais são as evidências disponíveis na literatura acerca da utilização da larvoterapia no tratamento de feridas de difícil cicatrização? Elegeram-se como critérios de inclusão: artigos originais, de revisão de literatura e de relatos de experiência, recorte temporal de 2016 a 2021, disponíveis *online* na íntegra, em português, inglês e espanhol e que respondessem à pergunta de pesquisa. Os critérios de exclusão foram: artigos duplicados, cartas ao editor, dissertações, teses, monografias e pesquisas com animais. Buscas ocorreram na Biblioteca Virtual em Saúde e Biblioteca Nacional de Medicina dos Estados Unidos entre agosto e setembro de 2021. **Resultados:** Selecionaram-se 10 artigos. As principais vantagens foram: desbridamento seletivo, ação bactericida ou bacteriostática e promoção de tecido de granulação e de fatores cicatrizantes. Já as principais desvantagens abrangeram: dor, desconforto, preconceito e fragilidades com o mercado de produção larval. **Conclusão:** As vantagens encontradas sobrepõem as desvantagens evidenciadas. Portanto, a larvoterapia é favorável para tratar feridas de difícil cicatrização.

DESCRITORES: Larva. Ferimentos e lesões. Terapêutica. Estomaterapia.

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LARVOTERAPIA EN EL TRATAMIENTO DE LESIONES DE DIFÍCIL CICATRIZACIÓN: REVISIÓN INTEGRADORA

RESUMEN

Objetivo: Analizar la evidencia disponible en la literatura sobre el uso de la larvoterapia en el tratamiento de heridas de difícil cicatrización. **Método:** Se trata de una revisión integradora, teniendo como pregunta orientadora: ¿cuál es la evidencia disponible en la literatura sobre el uso de la larvoterapia en el tratamiento de heridas de difícil cicatrización? Los criterios de inclusión fueron: artículos originales, revisión de la literatura y relatos de experiencia, período de tiempo de 2016 a 2021, disponibles en línea en su totalidad, en portugués, inglés y español y que respondieron a la pregunta de investigación. Los criterios de exclusión fueron: artículos duplicados, cartas al editor, disertaciones, tesis, monografías e investigaciones con animales. Las búsquedas se realizaron en la Biblioteca Virtual de Salud y la Biblioteca Nacional de Medicina de los Estados Unidos entre agosto y septiembre de 2021. **Resultados:** se seleccionaron 10 artículos. Las principales ventajas fueron: desbridamiento selectivo, acción bactericida o bacteriostática y promoción del tejido de granulación y factores de cicatrización. Las principales desventajas incluyeron: dolor, incomodidad, prejuicio y debilidades con el mercado de producción de larvas. **Conclusión:** Las ventajas encontradas superan las desventajas destacadas. Por lo tanto, la larvoterapia es favorable para tratar heridas de difícil cicatrización.

DESCRIPTORES: Larva. Heridas y lesiones. Terapéutica. Estomaterapia.

INTRODUCTION

It is estimated that 5% of adults in the Western hemisphere have at least one difficult-to-heal wound, and treatment of these types of skin lesions is often prolonged[1]. One survey found that the average time to treat difficult-to-heal wounds is around 9 years[2]. Another found patients with these types of wounds for more than 30 years, and the participants' treatment was based on topical dressings[3].

A study in the UK concluded that most existing proposals to treat difficult-to-heal wounds are ineffective and reflected on the costs surrounding the treatment of these injuries. According to the research, treating them costs an average of 2,410 pounds, an annual cost of around 5.3 billion pounds to the health care system[4].

As for Brazil, there are few studies on the incidence and prevalence of difficult-to-heal wounds, mainly regarding the macropopulation. The most recent pressure ulcer prevention protocol published by the Ministry of Health highlighted that the incidence rate for this type of injury is 39.81 in the country[5].

The types of treatment available in Brazil are mostly topical, which act locally and, therefore, have a slower action when compared to other more advanced technologies[3].

As in other countries, conventional therapies for the treatment of difficult-to-heal wounds bring impacts to the economy. Research conducted in an outpatient hospital in Minas Gerais showed a monthly expenditure of R$ 36,629.95 only to treat pressure sores[6]. Another study, in Rio de Janeiro, verified that a public outpatient service spent in 84 days R$ 2,264.98 to treat venous ulcers with topical coverage based on 2% carboxymethyl cellulose gel[7].

All this prolongation of the treatment of difficult-to-heal wounds, as well as the accompanying financial impact, signals a profound substantial unmet need in terms of treatment options[4].

Larval therapy, also known as biotherapy, biosurgery, or biodebridement[8], consists in the application of some species of live fly larvae, such as *Lucilia sericata* (Meigen), *Phormia regina* (Meigen), and *Lucilia eximia* (Wiedemann), after a process of rearing and disinfection in the laboratory, to treat wounds that are difficult to heal[9]. This controlled therapeutic myiasis is possibly an alternative to the problems already mentioned, because it is a low-cost, efficient, safe, feasible, and perhaps the only procedure that achieves cure and success[10].

Larval therapy is not a current therapeutic technique. It began to be applied many years ago. The first evidence of its use was in 1829, in injuries to commanders in Napoleon Bonaparte's army by Baron Dominique Larrey, a medical surgeon who was head of the army[10]. Later, another surgeon in World War I (1914–1918), Baer, based on observations on the battlefield, started breeding flies in the laboratory and introducing the larvae of these insects into the injuries of the wounded in battle. However, in the early years of applying larval therapy, the larvae were not sterile[11]. It was only in the 1930s that Baer implemented the first method of disinfecting fly eggs in his laboratory[9].

Thus, larval therapy began to be used in countries, however, because of the emergence of antibiotics in the early 1940s, it was forgotten. With the emergence of microbial resistance to antibiotics in the 1980s, larval therapy came back into use[9,10].

Thus, since the 1980s, several countries have reintroduced larval therapy into their territories to treat unhealed lesions, such as the United States of America, the United Kingdom, Israel, Switzerland, Germany, Sweden, Canada, Slovenia, Hungary, the Netherlands, Italy, Mexico, Belgium, Austria, and Ukraine[10].

In Brazil, there is no routine health care using larval therapy. Instead, there are experimental studies aimed at creating and extracting substances from fly larvae, research with the objectives of elaborating and standardizing methods of disinfection of fly eggs, and the development of studies with animals, such as mice[12].

The research developed was justified because the topic of larval therapy in difficult-to- heal wounds is little studied and disseminated in Brazil. Thus, the study may serve as one of the scientific foundations that will contribute to a possible start of larval therapy in wound treatment in the country.

The care of patients with wounds is a very relevant specialty in the nursing category. The stomal therapist is the professional who has knowledge, skills and competences acquired during the specialization to work with these patients. Therefore, this study can also contribute to the performance of nursing in its assistance to patients with wounds that are difficult to heal.

OBJECTIVE

To review the evidence available in the literature about the use of larval therapy in the treatment of difficult-to-heal wounds.

METHODS

This is an integrative review, which consists of synthesizing the knowledge already produced on a subject, encompassing and analyzing research with varied methodological approaches and making it possible to identify gaps in the literature on the subject studied so that new research can be developed[13].

The integrative review presents some steps, which guided the development of the study:

- Determining the topic and research question;
- Definition of the inclusion and exclusion criteria;
- Verification of the pre-selected and selected articles;
- Analysis and categorization of the included studies;
- Interpretation of the results;
- Synthesis of the information[14].

Thus, the guiding question was: what is the available evidence in the literature on the use of larval therapy in the treatment of difficult-to-heal wounds? It was developed according to the PICO strategy, where P refers to patient/problem; I, to intervention; C, to control/comparison; and O, to outcomes/endpoint. Through this strategy, it was also possible to map the terms in order to perform the database searches[15]. For this research, we chose to use free terms, dispensing with standardized and recognized terms, such as descriptors and keywords (Table 1).

Table 1. Construction of the guiding question according to the PICO strategy. Rio de Janeiro (RJ), Brazil, 2021.

Acronym	Definition	Description
P	Patient/problem	Patient with a difficult-to-heal wound
I	Intervention	Larval therapy
C	Control/comparison	-
O	Outcomes/endpoint	Wound healing

Source: Elaborated by the authors.

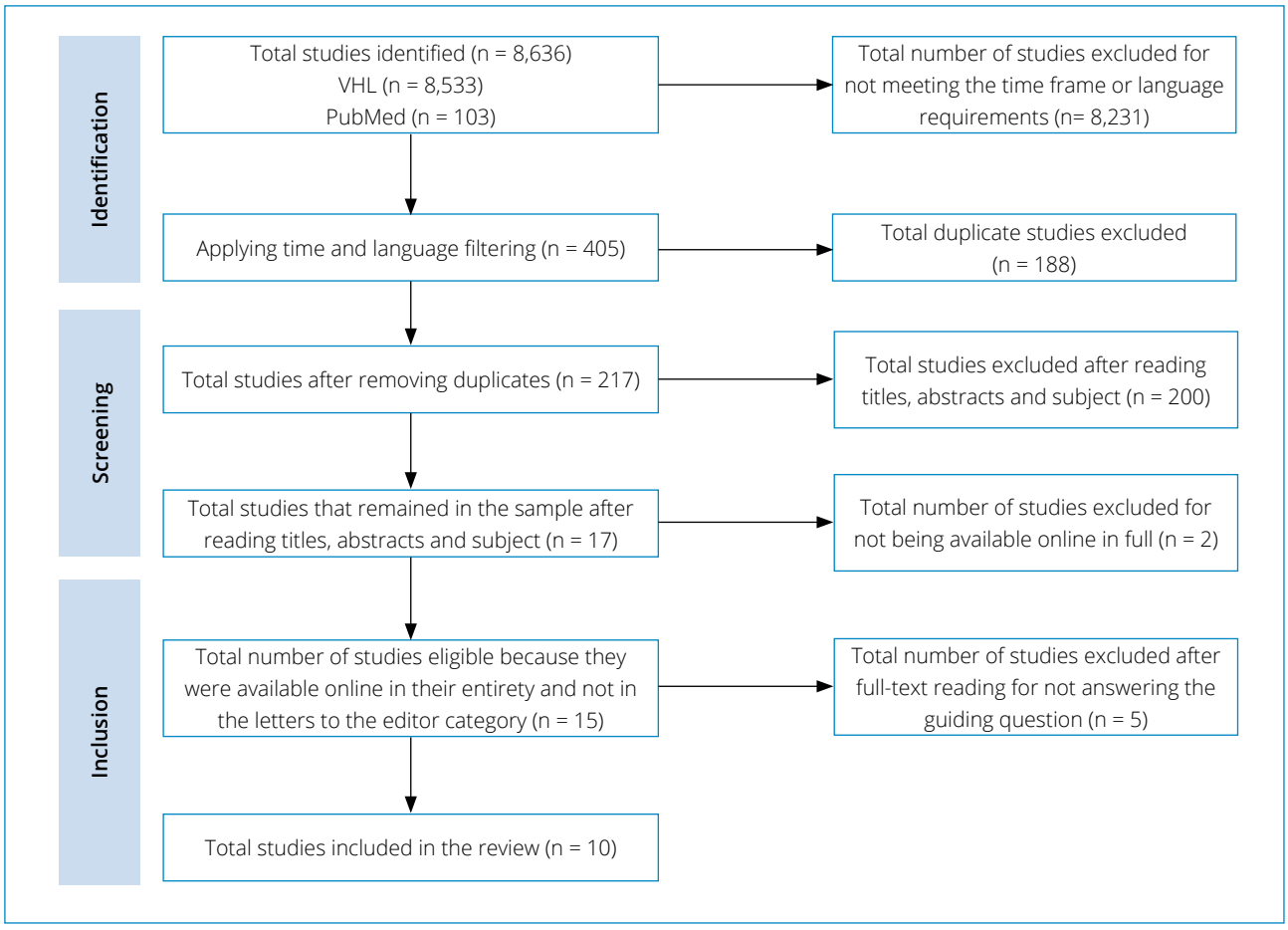
Inclusion criteria were: original articles, literature reviews, and experience reports, with a time frame of five years (2016 to 2021), available online in full, in Portuguese, English, and Spanish, and that answered the research question. Duplicate articles, letters to the editor, dissertations, theses, monographs, and research with animals were excluded.

The search took place from August to September 2021 in the Virtual Health Library (VHL), with the exception of the Medical Literature Analysis and Retrieval System Online (MEDLINE); and the United States National Library of Medicine (PubMed).

The free terms used were combined in different ways using the Boolean operator "OR." They are: "terapia larval," "terapia larval," "biodesbridamento," "bioterapia," "biocirurgia," "terapia larvaria," "biodesbridamiento," "biocirugía," "larval therapy," "larvotherapy," "biodesbridement," "biotherapy," "biosurgery," "maggot therapy," "maggot debridement therapy," "larva therapy," "larvotherapie," "larvo therapie," "larva therapie," e "larval therapy."

The selection of studies was carried out by the authors using Microsoft Excel software. Initially, 8,636 studies were identified as a result of the search using the free terms, of which 8,533 were from the VHL and 103 from PubMed. After applying the time frame and language criteria, 405 studies were selected. Of these, 188 were identified as duplicates, leaving 217. The reading of titles, abstracts and subjects discarded research on larval therapy in animal wounds, larval therapy in easy-to-heal wounds, or those that did not address larval therapy in wounds, totaling 200 excluded. Of the 17 studies then preselected, only 15 were available online in full and were not from the category letters to the editor. After exhaustive reading, only 10 articles that answered the guiding question remained, which made up the final sample of the review.

Importantly, the methodological quality of the studies was assessed independently by the authors and then discussed for consensus based on the Newcastle–Ottawa scale. That is, each study was scored from 0 to 9 in the three domains: selection of participants, similarity and comparability between groups, and verification of the outcome of interest between studies. Figure 1 shows the flow chart explaining sample selection, based on the PRISMA methodology. The pertinent data from the selected articles were extracted and categorized using an instrument created by the authors in Microsoft Excel software, containing the following information: title, authors, professional category of authors, language, country of origin of the research, year of publication, database, journal of publication, type of study, objective, main results, and conclusion Next, a simple descriptive analysis of the data was constructed, which were already grouped by categories. Finally, the knowledge synthesis was presented.



VHL: Virtual Health Library; PubMed: United States National Library of Medicine.

Figure 1. PRISMA flowchart of the review article selection process. Rio de Janeiro (RJ), Brazil, 2021.

Source: Elaborated by the authors.

RESULTS

The final sample consisted of 10 articles, which were summarized and characterized in Table 2.

Table 2. Characterization and synthesis of the studies included in the review. Rio de Janeiro (RJ), Brazil, 2021.

Article identification	Authors / professional category of authors	Language / country of research origin / year / database	Journal	Type of study	Objective	Conclusion
A1[16]	Trujillo et al. / nursing team	Spanish Research's country: was not mentioned. Journal's country: Uruguay 2016 BVS	*Revista Uruguaya de Enfermería*	Integrative review	Finding alternative and conventional measures for the treatment of venous ulcers.	The various techniques pointed to a similar scarring result. The alternative therapies had a lower economic value, but the treatment time was longer. Unconventional products have shown good results.

continue...

Table 2. Continuation...

Article identification	Authors / professional category of authors	Language / country of research origin / year / database	Journal	Type of study	Objective	Conclusion
A2[17]	Arabloo et al. / unspecified healthcare professionals	English Research's country: was not mentioned. Journal's country: Iran 2016 PubMed	*Medical Journal of the Islamic Republic of Iran*	Systematic review	Systematically evaluate the safety, efficacy and economics of larval therapy in comparison with other conventional treatments for the treatment of wounds and ulcers in the wound and ulcer patient population in light of predefined outcomes.	Larval therapy showed many benefits, such as: decreased rate of amputations, fewer side effects, accelerated debridement of the lesion, bactericidal action, pain control, and wound healing.
A3[18]	Blanco / nurse	Spanish Research's country: was not mentioned. Journal's country: Spain 2017 BVS	*Revista Internacional de Ciencias Podologicas*	Integrative review	Discover the treatments used by nursing to treat diabetic foot.	Among the most innovative therapies, ozone therapy stood out for the treatment of diabetic foot. There are no protocols in the literature on which therapy to choose to treat diabetic foot, and they must be adjusted to the needs and characteristics of each patient.
A4[19]	Raposio et al. / unspecified professionals	English Research's country: was not mentioned. Journal's country: USA 2017 PubMed	*Wounds*	Integrative review	Review the history and mechanisms of action of larval therapy and speculate on some future directions.	Further in vivo studies are needed to verify new larval species for use in larval therapy, as well as to identify the cost-effectiveness of each.
A5[20]	Stadler / biochemist	English Research's country: was not mentioned. Journal's country: Austria 2020 PubMed	*Medical and Veterinary Entomology*	Integrative review	Bringing together disparate but connected lines of research in order to build a coherent first-pass theory of the larval therapy supply chain.	The literature has not yet discussed the provision of larval therapy services containing conceptual and disciplinary framework of supply chain management, neither in healthcare practice nor in committed healthcare settings. There is little knowledge in the public domain about the transport and distribution of larvae.

continue...

Table 2. Continuation...

Article identification	Authors / professional category of authors	Language / country of research origin / year / database	Journal	Type of study	Objective	Conclusion
A6[21]	Lipiński et al. / medical team	English Poland 2020 PubMed	*Journal of Wound Care*	Case study	To search the literature for findings that explain what happened, that is, phantom pain as an adverse event of larval therapy.	It has been suspected that the larvae contain salivary substances with the ability to activate nerve regeneration; however, the mechanisms of nerve regeneration are intricate, obscure and need further research.
A7[22]	Silva et al. / nursing staff and librarian	Portuguese Brazil 2020 VHL	*Estima Brazilian Journal of Enterostomal Therapy*	Exploratory research	To describe the perception of patients with difficult-to-heal wounds submitted to larval therapy.	Patients have stated many advantages of larval therapy, some of them being: reduced pain and odor, improved lesion, faster wound healing, and feelings of hope to live again. They also expressed some disadvantages of the technique, such as seething/tingling, by the movement of the larvae in the lesion, and repulsion of the patient and healthcare professional. Despite this, larval therapy was judged by those surveyed as optimal, especially with regard to the efficacy of debridement of necrotic tissue without the need for other types of debridement.
A8[23]	Nair et al. / unspecified healthcare professionals	English Malaysia 2021 PubMed	*International Journal of Lower Extremity Wounds*	Case study	Describe the processes of larval therapy in Malaysia.	Larval therapy ensured health equity, since it easily reached the geographically disadvantaged groups.
A9[24]	Greene et al./ nursing team	English Research's country: was not mentioned. Journal's country: Netherlands 2021 PubMed	*Journal of Tissue Viability*	Systematic review	To determine the effect that larval therapy has on wound debridement.	Larval therapy promoted rapid debridement of non-viable tissue and was a resource-effective method; however, the study did not indicate that larvae had the ability to increase the rate of healing. The treatment was able to increase the pain level of the injury sufferers, but the pain was shown to reduce from baseline after the treatment was completed. Prejudice still discredits the evidence found in the literature.

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Table 2. Continuation...

Article identification	Authors / professional category of authors	Language / country of research origin / year / database	Journal	Type of study	Objective	Conclusion
A10[25]	Szczepanowski et al. / unspecified healthcare professionals	English Poland 2021 PubMed	*International Wound Journal*	Clinical trial	To evaluate changes in microflora in patients treated with *L. sericata* larvae for diabetic leg and foot ulcers.	The efficacy of larval therapy in lower limb ulceration and diabetic foot in individuals with compensated diabetes was found by observing the rearrangement of the microflora in the wounds, but new studies are needed for a more precise evaluation of its efficacy, with a larger number of participants and the use of molecular biology methods.

VHL: Virtual Health Library; PubMed: United States National Library of Medicine.

Source: Elaborated by the authors.

Regarding the professional category of the authors, 40% (n = 4) identified themselves as unspecified health professionals, 30% (n = 3) as nursing staff members, 10% (n = 1) of the nursing staff with a librarian partnership, 10% (n = 1) of the medical staff, and 10% (n = 1) as a biochemist.

Regarding language, the prevalence of English (70%, n = 7) was noticed, followed by Spanish (20%, n = 2), and lastly Portuguese, (10%, n = 1). Of the articles that comprised the research, only 10% (n = 1) were Brazilian, the others being of international origin.

Based on the cut-off time, 20% (n = 2) of the articles were published in 2016, 20% (n = 2) in 2017, 30% (n = 3) in 2020, and 30% (n = 3) in 2021.

About the databases, 70% (n = 7) of the studies were indexed in PubMed and only 30% (n = 3) in the VHL.

Finally, regarding the types of studies that comprised the sample, 40% (n = 4) were primary research and 60% (n = 6) were secondary.

The analysis of the articles allowed us to compose the following thematic categories: indications for larval therapy, health contexts of larval therapy, and advantages and disadvantages of larval therapy, which are discussed below.

DISCUSSION

The four pillars that make up the information synthesis are discussed below.

Indications of larval therapy

The present study showed that larval therapy can be applied to several types of lesions, and is a very comprehensive technique[19].

Among the types of injury most cited by the studies analyzed, diabetic foot, venous ulcer and pressure injury were the main indications found, when it comes to etiology[16-19,21-25]. In addition, larval therapy was also highly oriented in cases of infected and/or necrotic wounds[16,17,19,21,25].

Other recommendations for larval therapy were identified in the sample, such as burns[24], traumatic wounds[19,21], soft tissue injuries[21], arterial ulcer[17,19,21,25], postoperative wounds[21], and also as a form of wound bed preparation prior to surgical closure[17,19].

In some cases, larval therapy became indispensable, as in intractable wounds, in individuals who were resistant to antibiotics, or in those who could not tolerate medication, whether these wounds were acute or chronic[17,21,23].

Health contexts of larval therapy

Based on the health contexts, more specifically the health settings in which larval therapy can be applied, a scarcity on this subject was observed in the identified articles. Thus, only four articles in the sample considered it relevant to mention it[21-23,25].

The most commonly observed context for the use of larval therapy was the outpatient service, being cited in all four surveys. The hospital setting was the second most common in the sample[22,23], followed by clinics and primary care units[23].

There are also other scenarios beyond the limits of this paper. According to a case study of larval therapy in the home, use in this setting has been shown to be safe, quick, and effective[26].

The advantages of larval therapy

From the articles reviewed, it was found that larval therapy has several benefits. The main feature of the technique, evidenced in 80% of the articles, is debridement[16,17,19-24]. This removal of necrotic tissue occurs quickly, selectively, and without bleeding, occurring mechanically and enzymatically. As the larvae crawl along the wound bed, they make perforations in the necrotic tissue with their mouth hooks. This facilitates their enzymatic debridement, because it increases the contact surface of proteolytic enzymes present in the salivary secretions of the larvae, transforming the necrotic tissue into a liquefied form, for subsequent absorption and digestion by the larvae[16,17,19-21,23,24].

The article A4[19] brought a comparison of larval therapy with hydrogel in desquamative venous ulcers, demonstrating that larval therapy led to effective debridement of the lesion in all patients undergoing therapy, as well as being a low-cost procedure, since larval therapy required a single application, while the other required a month to fulfill its effect.

The study A9[24], similarly to A4[19], also pointed out comparisons of larval therapy with hydrogel. Although their findings showed that larval debridement was faster, the research found that after seven to 14 days only 29% of larval debrided wounds remained necrosis-free, while 73% of hydrogel debrided lesions remained unchanged, leading the authors to consider an extreme difference.

The second main characteristic found in larval therapy was its important action against bacteria, including multidrug-resistant bacteria, present in 70% of the studies[16,17,19,20,23-25]. The bactericidal effect occurs through the ingestion of bacteria, through the action of antimicrobial peptides present in salivary secretions that lead to the death of gram-negative and gram-positive bacteria, including those with resistance to antibiotics, such as methicillin-resistant *Staphylococcus aureus*[19,23,25,27]. There are also intestinal excreta from the larvae, which also degrade bacteria when released into the lesion. In other words, the larvae have bactericidal mechanisms from the beginning to the end of their digestive tract[23].

It is important to emphasize that this bactericidal effect caused by the larvae leads to a decrease in inflammation, edema, pain, and odor in the lesion[22].

Salivary secretions also control or inhibit the proliferation of microorganisms, leading to bacteriostatic action through proteolytic enzymes, which alkalize the pH of the lesion bed[19,25].

Another way the bacteria control the larvae is by increasing exudate that washes the pathogens out mechanically by rinsing them from the wound[23].

Therefore, another advantage of larval therapy is that it makes it possible to decrease the use of antibiotics, minimizing antibiotic resistance, which is currently a global health problem, and also reducing mortality from septic shock[23].

The third and fourth main characteristics of larval therapy are the promotions of granulation tissue[16,19,23,24] and wound healing[17,18,22,23], both of which were evident in 40% of the sample.

The formation of granulation tissue occurs by the very movement of larvae under the wound bed, which stimulate angiogenesis, increasing oxygen supply[23,25]. The proliferative phase is also stimulated by secretions and hemolymph of the larvae, which contain epidermal growth factor or interleukin 6, capable of increasing the development of fibroblasts in wounds[19].

About the effective healing factors promoted by the larvae, one can mention the secretion of healing and anti-inflammatory substances in the wound bed. In addition, the larvae have the ability to stimulate tissue regeneration, promoting cell activity and wound contractility[19,20,23,24].

Regarding healing time, articles A2[17] and A3[18] stated that the use of larval therapy was shown to be effective and lead to complete wound healing faster than other conventional therapies. Another study echoed that statement, reporting that larval therapy improves the lesion by rapid healing[22]; however, research A3[18] came to the conclusion that among the unconventional practices, ozone therapy is the most advantageous for healing diabetic foot.

The A9[24] paper, on the other hand, when comparing hydrogel with larval therapy, found that even though larval therapy heals a little faster, the differences in time interval between the two techniques were minimal.

The main characteristics of larval therapy, mentioned above, lead to some secondary advantages, such as: reduction of amputations or even an increase in the possibility of maintaining part of the limb, reduction of limitations in performing day-to-day activities, increased belief in the cure of the injury, improved self-esteem and quality of life for the patient, and the appearance of hope for the return of their lives[17-19,22,23].

There are other benefits that larval therapy provides, besides those for the patient, related to the functioning of the service to be provided, its procedures and impacts, in other words, advantages for the professional, for the institution, for the market and for the health system. The final words of this pillar were aimed at these advantages. Thus, one can cite: easy application, cost-effectiveness, and cost reduction of hospitalization and treatment of wounds that are difficult to heal, since the inputs spent to perform the dressing in larval therapy are minimal compared to other conventional methods[17,23,24].

In addition, there is a reduction in the demand for nursing care and dressing changes, since an application is valid for up to 72 hours, reduction in the time of care to perform the dressing, and less frequency of outpatient appointments[17,19,20,24]. It is also possible to use the larvae as many times as necessary, free or bagged in biobag membranes, increasing acceptance and deconstructing prejudice[20]. Finally, there is a market with great potential to be explored, which has a simplified in vitro larval rearing process[19,20].

The disadvantages of larval therapy

About 90% of the studies pointed out disadvantages regarding larval therapy, which are described below[16-22,24,25].

When it came to unwanted effects of larval therapy, the possibility of pain brought with it controversy. Pain was the most identified side effect in the sample, totaling 40%[17,20,21,24]. Studies have stated that larval therapy induces pain and increases existing pain[20,24].

The article A6[21] brought up a rare case of pain caused by this therapy: phantom pain caused by a kind of poorly understood nerve regeneration, which triggered severe pain that did not cease with the use of opioids However, another study found that, although pain is present, it can subside after the first 24 hours or after the first removal, and is a transient side effect. The same article also reported that larval therapy, when compared to other common methods, had fewer undesirable effects and was therefore safer[17].

In contrast to this disadvantage, A7[22] reported in his field research that such a procedure was painless for all patients undergoing the technique, including people with and without diabetes.

Besides pain perception, there are also other sensory perceptions that can be brought up during the practice. These manifest as a kind of tingling, scratching, pruritus, itching, which can be explained by the movement of the larvae under the

bed of the lesion[22]. It is important to stress that the study did not find these perceptions in some individuals with diabetes mellitus, perhaps because of the decreased sensitivity due to the clinical condition of the disease itself.

The article that highlighted phantom pain from larval therapy also identified sensations of burning, crushing, and electric shock[21].

Some studies have stated that these undesirable effects did not impede the performance of daily activities[17,22], although the A6[21] study proved contrary to these findings.

These disadvantages were the main causes of dropout, a major problem when it comes to larval therapy[21,24].

Another detriment of larval therapy found in the sample was the uncertainty of whether the therapy had properties to subsist alone. Article A1[16] stated that the therapy was not able to finish the healing process of venous ulcers without being associated with other therapies. Blanco[18], on the other hand, found that larval therapy needed to be associated with the use of antibiotics to heal more quickly.

Another concern from A1[16] was about the wound being prone to new infections after debridement, as the bacteria were not eliminated physiologically with proper production of memory antibodies.

On the contrary, A4[19] stated that although larval therapy showed positive effects for healing independently, this was not the only determining factor for, therefore, there are factors other than the edges of the lesion, such as: pressure and humidity control in pressure sores, glycemic control in diabetic feet, among others.

Regarding the forms of presentation of larval therapy, the larvae arranged freely in the lesion bed are more likely to trigger sensory effects, in addition to leakage, when the dressing is not properly protected. The bagged ones, on the other hand, have slower debridement because the wound-lesion contact area is reduced[20].

Another disadvantage of larval therapy perceived by A10[25] was the fact that the larva of the species L. sericata presents greater bactericidal efficacy against gram-positive bacteria than gram-negative ones, with the main gram-negative bacteria that are more difficult being: Enterobacteriaceae, *Corynebacterium, Pseudomonas aeruginosa, methicillin-sensitive S. aureus*, and negative *Streptococcus coagulase*[25]. This occurs because gram-negative bacteria secrete endotoxins capable of neutralizing the antimicrobial peptides present in larval secretions. Therefore, it is necessary to use a larger number of larvae for a bactericidal effect on these bacteria[25].

The authors also state that prolonging the treatment time of larval therapy led to an increase in the number of gram-negative bacteria in the wound, hindering the healing process, but the research stated that there is a need for further studies to know whether this increase was due to the gradual loss of efficacy of the larvae or to their death. The latter case can be explained by the fact that the larvae have in their intestinal microflora gram-negative bacteria, *Proteus mirabilis*, which protect the larvae from pathogenic microorganisms[25].

As for the larvae production market, it has shown to be limited and uninterested. Faces such as the deadline for application within 48 hours after distribution in service units, which must coincide with demand, are one of the processes that demotivate the private market, hindering its expansion. Thus, difficulties such as loss of larvae timely and interruption of treatment due to lack of larvae are possible[19,20,22].

The market, in general, is still restricted in what concerns the larval range, directed mostly to only two larval species, *Lucilia cuprina* and *L. sericata*. There is a need for new in vivo research to identify other species that can add to the technique, filling gaps such as the short shelf life of the product after distribution, and its cost-effectiveness[19].

There are also disadvantages, beyond the fields of an injury, referring to culture, living conditions, breeding, which imply the acceptability of larval therapy. Findings such as repulsion and aversion of both the patient to the therapy and the professional who applies it contribute to a scenario of prejudice, which discredits the scientific evidence[22,24].

It was evidenced that the patient's openness towards larval therapy was relative and suffered circumstantial influences. According to study A7[22], acceptance is linked to the strong desire for a cure, the risk of a possible imminent amputation, the hopelessness with regard to conventional treatments, besides the breaking of stigmas through guidance and clarification by the professional. In other words, acceptability is a matter of conversation, sensitive listening, and respect.

As a limitation of the research, there was a scarcity of studies on larval therapy developed in Brazil, and most of the findings that comprised this research were literature reviews.

Therefore, new field research studies with methodological rigor, such as clinical trials with low risk of bias, especially in Brazil, are recommended, since there is a need for greater understanding of how the practice is done in the Brazilian reality, with financial investment for this purpose.

CONCLUSION

This study was designed to answer a question about the topic of larval therapy in difficult-to-heal wounds, and the objective was To review the evidence available in the literature about the use of larval therapy in the treatment of difficult-to-heal wounds.. According to the methodology applied, the results and the discussion of this research, it could be concluded that the objectives were fully achieved.

According to the limits of this work, it was possible to understand that larval therapy is an ancient practice of low cost, comprehensive, which meets various needs. It has easy application, which allows multiple scenarios of action, such as home care to hospitalization, and scientifically proven effectiveness in debridement, infection control, stimulation of granulation tissue and other healing factors.

It is important to point out that there are undesirable effects, the main ones being pain and discomfort, which increase the risk of dropout, besides the historically embedded prejudice. There are also weaknesses regarding the supply by the market and demand in health services. The findings also did not guarantee total control of bacterial infections from gram-negative bacteria.

The advantages found in the present study outweigh the disadvantages also highlighted here, since these only bring temporary harm. Larval therapy is favorable for the treatment of difficult-to-heal wounds.

The research contributed to professional training and qualification (teaching), as it presented an alternative and effective measure for the treatment of difficult-to-heal wounds, and could be understood and discussed by students in training and by professionals. It also brought contributions to the production of knowledge (research) on larval therapy, as it brought together elements and filled gaps about its use and the circumstances surrounding it, besides having relevance for Brazilian research, since there was a lack of studies on the subject in Brazil. Finally, it contributed to the assistance and valorization of health not only locally, but possibly worldwide, when it comes to the treatment of difficult-to-heal wounds, and may also in the future be one of the scientific foundations for the initiation of larval therapy in the country.

AUTHORS' CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Ferreira LFSL, Figueiredo RMP, Oliveira LS, Vieira RPC, Leal EPBV, Pereira JD, Abreu AM e Figueiredo RAR; Conception and design: Ferreira LFSL, Figueiredo RMP, Oliveira LS, Vieira RPC, Leal EPBV, Pereira JD, Abreu AM e Figueiredo RAR; Data collection, analysis and interpretation: Ferreira LFSL, Figueiredo RMP, Oliveira LS, Vieira RPC, Leal EPBV e Pereira JD; Article writing: Ferreira LFSL, Figueiredo RMP, Oliveira LS, Vieira RPC, Leal EPBV, Pereira JD, Abreu AM e Figueiredo RAR; Critical review: Ferreira LFSL, Figueiredo RMP, Oliveira LS, Vieira RPC, Leal EPBV, Pereira JD, Abreu AM e Figueiredo RAR; Final approval: Abreu AM e Figueiredo RAR.

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