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REGENERATIVE POTENTIAL OF TASPINE DERIVED FROM CROTON LECHLERI: A NARRATIVE REVIEW

POTENCIAL REGENERATIVO DA TASPINA DERIVADA DE *CROTON* LECHLERI: UMA REVISÃO NARRATIVA

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ABSTRACT

Dragon's blood resin (*Croton lechleri*) is a natural product used in traditional medicine as a wound healer. It is believed that taspine, derived from the resin, is the phytochemical component with the highest activity in tissue repair. The aim of this study was to conduct a narrative review of the regenerative potential of the bioactive taspine present in the resin. A search was conducted in the databases PubMed, SciELO, and Google Scholar, using the descriptors: dragon's blood, taspine, wound healing, and bioactives. Inclusion criteria were applied to articles of the case report, experimental, and systematic review types, with no temporal filter. Exclusion criteria eliminated duplicate publications or those outside the thematic scope. Of the 273 articles retrieved, only 17 studies composed the sample. Despite the diversity of substances present in the resin, taspine, the alkaloid, was predominant. The literature highlights its beneficial characteristics of healing action, favored by fibroblast chemotaxis, collagen fibrogenesis, angiogenic and epithelial proliferation. However, the tissue repair profile beyond the skin remains unexplored, particularly due to a lack of preclinical biological studies with the natural resin, stemming from vegan and cruelty-free principles. It can be concluded that taspine shows excellent potential for cutaneous regeneration, suggesting the need for more studies on bioactivity either in isolation or in combination with biomaterials.

Keywords: Croton. Phytochemicals. Alkaloids. Regeneration. Tissue Engineering.

RESUMO

A seiva de sangue de dragão (*Croton lechleri*) é um produto natural usado na medicina tradicional como cicatrizante. Acredita-se que a taspina derivada da seiva seja o componente fitoquímico com maior atividade no reparo tecidual. O objetivo deste estudo foi realizar uma revisão narrativa do potencial regenerativo do bioativo taspina presente na seiva. Foi realizada uma busca nas bases de dados PubMed, Scielo e Google Acadêmico, com os descritores: sangue de dragão, taspina, cicatrização de feridas e bioativos. Adotou-se como critérios de inclusão artigos do tipo relato de caso, experimentais e revisões sistemáticas, sem filtro temporal. Como critérios de exclusão, foram eliminadas publicações duplicadas ou fora da temática. De 273 artigos recuperados, apenas 17 estudos compuseram a amostra. Apesar da diversidade de substâncias presentes na seiva, houve prevalência do alcalóide taspina. A literatura destaca suas características benéficas de ação cicatrizante, favorecida por quimiotaxia de fibroblastos, fibrogênese colágena, proliferação angiogênica e epitelial. Entretanto, o perfil de reparo tecidual além da pele permanece desconhecido, em especial por carência de estudos biológicos pré-clínicos com a seiva natural, decorrente de princípios veganos e livres de crueldade. Pode-se concluir que a taspina mostra excelente potencial para a regeneração cutânea, sugerindo mais estudos sobre a bioatividade isolada ou em associação com biomateriais.

Palavras-chave: Croton. Compostos Fitoquímicos. Alcaloides. Regeneração. Engenharia Tecidual.

INTRODUCTION

Brazilian biodiversity comprises an immense number of plant species with medicinal properties, constituting a centuries-old wealth that is still widely used for the prevention and treatment of diseases in vulnerable communities (Lepsch-Cunha *et al*, 2024). However, many of these plants have not been studied and their therapeutic mechanisms are not fully understood (Azevedo *et al*, 2008). Phytotherapy and the use of medicinal plants comprise a practice named traditional

medicine, which declined in the 1940s and 1950s due to the process of industrialization (Bruning; Mosegui; Vianna, 2012). However, it has rekindled interest in advances in the development of safe and effective herbal medicines, in response to the population's search for less aggressive and more natural therapies (Yunes; Pedrosa; Cechinel-Filho, 2001).

Due to the growing interest in ethnopharmacological research focused on the relationship between natural products and their applications in the health field, the Brazilian government regulated the National Policy on Medicinal Plants and Herbal Medicines, which establishes guidelines and actions related to the production of herbal medicines and medicinal plants (Brasil, 2009). The Ministry of Health promoted research on medicinal plants with the potential to develop herbal medicines for use in the Unified Health System (SUS) with the publication of the National List of Medicinal Plants of Interest to the SUS (Renisus). This list includes plant species used popularly and with scientifically proven efficacy, and the genus Croton is listed in Renisus, represented by the species *Croton cajucara* and *Croton zehntneri* (Brasil, 2009).

Croton lechleri Müll. Arg., a tree from the Euphorbiaceae family, widely found in the Amazon region of countries such as Peru, Ecuador, Brazil, Bolivia, and Colombia, has not yet been listed due to a lack of conclusive research proving its safety and efficacy (Porras-Reyes *et al*, 1993; Silva, 2015; Uchida, 2023). It is popularly known as dragon's blood due to its viscous, dark red sap (Pieters *et al*, 1995; Rossi; Souza; Machado, 2023; Uchida, 2023).

Interest in the properties of dragon's blood latex is justified by the presence of high levels of secondary metabolites in the sap that exhibit bioactivity, including alkaloids, diterpenes, and phenolic compounds (Hidalgo *et al*, 2018; Londoño-Lemos; Bustamante, 2019; Monterubbianesi *et al*, 2023; Rossi; Souza; Machado, 2023). Among the most frequent components, taspine has been highlighted; it is an alkaloid and has been reported to actively participate in the repair process in different cell lines (Azevedo *et al*, 2008; Porras-Reyes *et al*, 1993; Vaisberg *et al*, 1989). The effects of pure dragon's blood sap are multifaceted, including potential antimicrobial, anti-inflammatory, antioxidant, analgesic, and antitumor properties, as well as its use in treating gastrointestinal disorders and promoting wound healing (Hidalgo *et al*,

2018; Londoño-Lemos; Bustamante, 2019; Martel; Buitrón; Bernardo, 2019; Monterubbianesi *et al*, 2023; Namjuyan *et al*, 2015; Pieters *et al*, 1995; Rossi; Souza; Machado, 2023; Vasconcelos *et al*, 2024).

Given the lack of knowledge about the detailed action of this bioactive compound, the aim of this narrative review was to seek an understanding of the mechanisms by which taspine modulates the tissue regeneration process.

METHODOLOGY

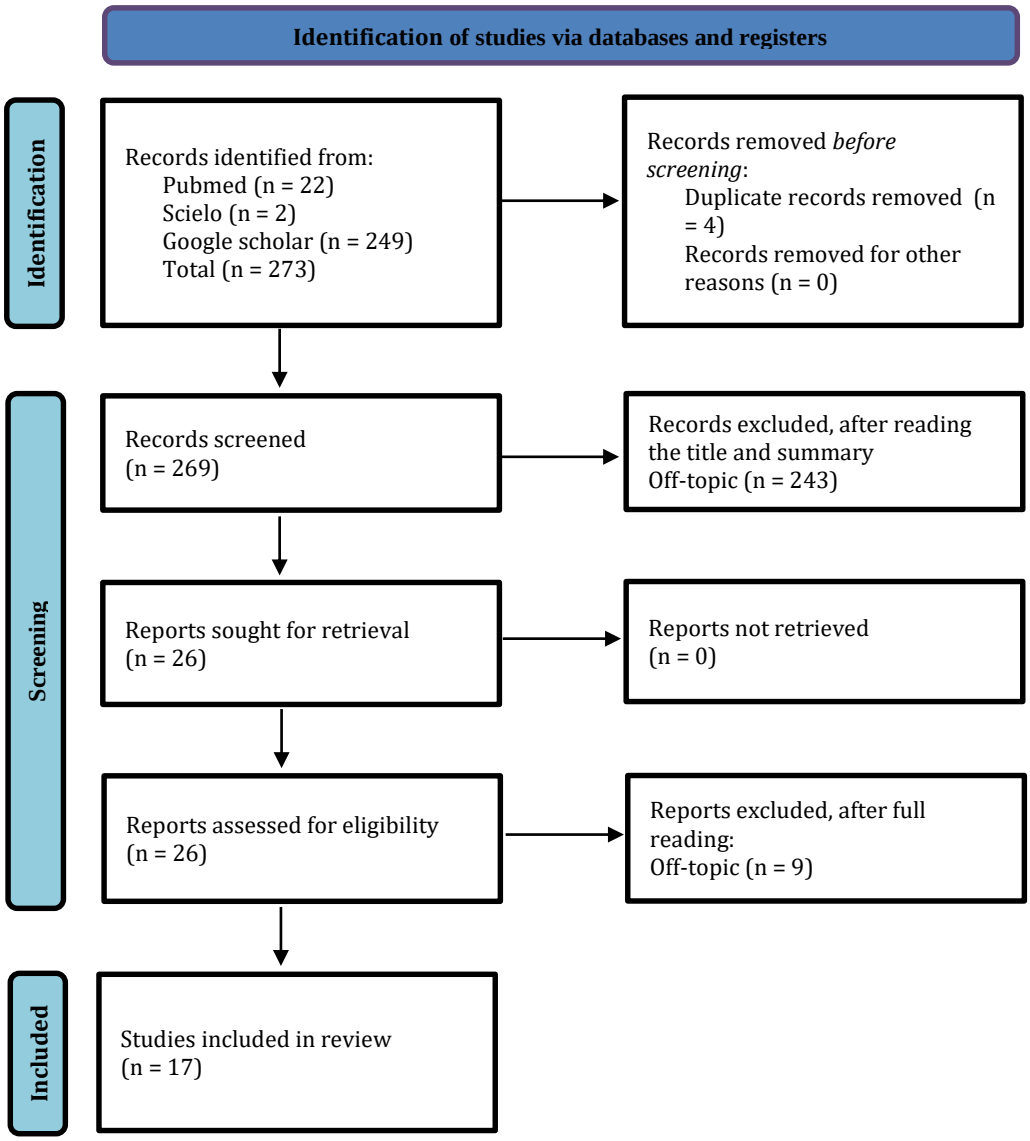
A narrative review was conducted, guided by the question: "What is the role of the bioactive taspine in tissue regeneration?". The search for articles was carried out in three electronic databases: PubMed, SciELO, and Google Scholar, without temporal filtering. The search strategy combined the following keywords: *Croton lechleri*, Croton, taspine, wound healing, and bioactives, associated with the Boolean operators "AND" and "OR".

Studies were selected that met the previously established criteria, which included: original research, whether conducted *in vitro* or *in vivo*, clinical trials, complete case reports, and systematic reviews, published between 2015 and 2025; availability of full texts in languages such as Portuguese, English, or Spanish. On the other hand, studies categorized as editorials, letters to the editor, or book chapters, duplicate publications, or those that did not have access to the full text were excluded.

RESULTS

Of the two hundred and seventy-three references retrieved, only seventeen studies comprised the final sample (Figure 1).

Figure 1: Flowchart for study eligibility for narrative review.



Source: Research data.

The literature consulted unanimously confirmed the hypothesis that taspine is the main healing bioactive compound present in dragon's blood sap (Azevedo *et al*, 2008; Chambilla; Vásquez, 2007; Hidalgo *et al*, 2018; Londoño-Lemos; Bustamante, 2019; Lopes *et al*, 2013; Martel; Buitrón; Bernardo, 2019; Monterubbianesi *et al*, 2023; Namjuyan *et al*, 2015; Pieters *et al*, 1995; Porras-Reyes *et al*, 1993; Rossi; Souza; Machado, 2023; Silva, 2015; Silva *et al*, 2019; Uchida, 2023; Vaisberg *et al*, 1989; Vasconcelos *et al*, 2024; Wang; Gao; Sun, 2021). Few bibliographic sources have focused specifically on the study of taspine (Chambilla; Vásquez, 2007; Londoño-Lemos; Bustamante, 2019; Lopes *et al*., 2013; Martel; Buitrón; Bernardo, 2019;

Monterubbianesi *et al*, 2023; Namjuyan *et al*, 2015; Pieters *et al*, 1995; Porras-Reyes *et al*, 1993; Rossi; Souza; Machado, 2023; Vaisberg *et al*, 1989; Vasconcelos *et al*, 2024; Wang; Gao; Sun, 2021) and it was the main limitation found in this review.

The alkaloid taspine exhibits an in vitro effect of not affecting cell proliferation and not generating toxicity to skin fibroblasts at concentrations below 150 ng/mL, and a dose-dependent *in vivo* wound healing action for an effective dose of 0.375 mg/kg. No carcinogenesis-promoting activity was reported in mice up to 17 months of treatment, confirming its biological safety (Vaisberg *et al*, 1989).

The topical effects of taspine on wound healing were verified in rats, where a single topical application of taspine (250 µg) significantly accelerated the initial phases of tissue repair, increasing the tensile strength of the wound distension by 26% on the fifth day and by 30% on the seventh day after injury compared to the control (Porras-Reyes *et al*, 1993). The mechanism by which taspine modulates cutaneous wound coaptation appears to be especially related to its chemotactic properties directed at fibroblasts, which migrate to the central area of the lesion and could explain wound contraction during healing (Porras-Reyes *et al*, 1993). Thus, fibroblast migration appears to be its most characteristic mechanism of action (Londoño-Lemos; Bustamante, 2019; Monterubbianesi *et al*, 2023; Rossi; Souza; Machado, 2023). Histological analysis of wounds treated with taspine in rats shows a marked increase in fibroblast density compared to mononuclear cells, characterizing a limited physiological inflammatory period and a more evident acceleration of the pro-repair mechanism (Porras-Reyes *et al*, 1993).

Taspine also influences other crucial aspects of the tissue regeneration process linked to the connective extracellular matrix. When rats were treated with taspine hydrochloride, the content of hydroxyproline, an indicator of collagen, was significantly higher, differing from the more persistent scar granulation tissue of the controls, suggesting that taspine stimulates fibrogenesis *in situ* (Pieters *et al*, 1995; Wang; Gao; Sun, 2021).

A study using taspine hydrochloride in rats explored its relationship with keratinocyte growth factor (KGF), suggesting that the promotion of wound healing by taspine hydrochloride may be closely related to the regulation of KGF expression in granulation tissue and subsequent stimulation of epitheliogenesis, as well as a

significant increase in angiogenesis, due to the increased number of newly formed capillaries in the initial phase of tissue repair in wounds treated with the bioactive compound (Wang; Gao; Sun, 2021).

Taspine shows a positive and multiple effect on tissue repair, although it exhibits fewer effects than pure dragon's blood sap, lacking the more characteristic antioxidant potential of its other polyphenolic components (Rossi; Souza; Machado, 2023). In addition to its remarkable wound-healing properties, taspine demonstrates anti-inflammatory, antitumor, antibacterial, antiviral, and cytotoxic activities (Hidalgo *et al*, 2018; Londoño-Lemos; Bustamante, 2019; Rossi; Souza; Machado, 2023; Vasconcelos *et al*, 2024; Wang; Gao; Sun, 2021). The broad therapeutic coverage indicates the need for more in-depth studies for each intended purpose, which were not the subject of this review.

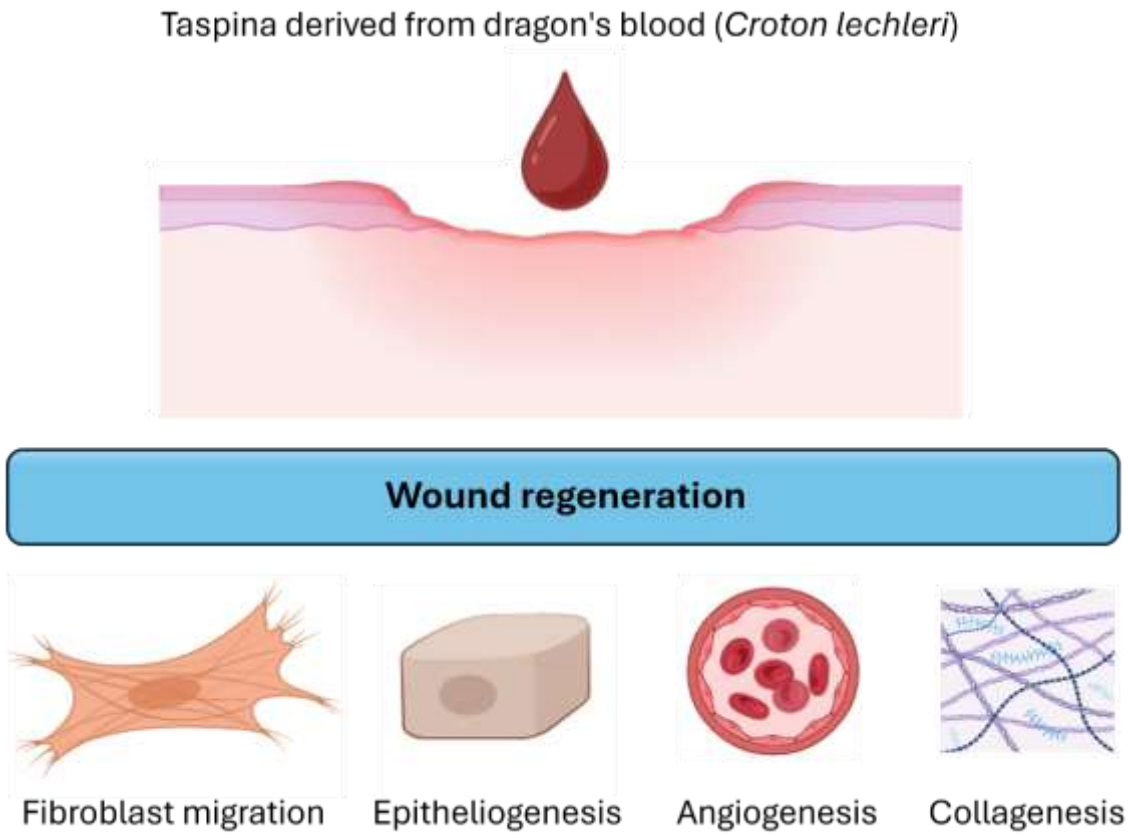
When considering profiles for clinical applications, ranging from aesthetic skin improvements against aging, reducing wrinkles and facial expression lines (Namjuyan *et al*, 2015; Rossi; Souza; Machado, 2023) to patients with more difficult skin healing, such as diabetic ulcers (Silva, 2015; Silva *et al*, 2019), these would be an appropriate therapeutic target for the bioactive compound taspine. A randomized clinical trial with a cream containing 15% ethanolic extract of *C. lechleri* revealed a significant improvement in skin marks as early as the third day of treatment up to 20 days of follow-up, attributing this property to phenolic compounds and the alkaloid taspine (Namjuyan *et al*, 2015). Studies on chronic ulcers in diabetic patients in the lower limb region using a 10% *C. lechleri* sap ointment have demonstrated a significant correlation between treatment time and wound size, suggesting the ointment's effectiveness in skin healing without active infection (Silva, 2015, Silva *et al*, 2019).

Dentistry represents a very promising area, with applications of dragon's blood containing taspine and other metabolites for the treatment of oral mucosal lesions, such as the correction of gingival fissures (Monterubbianesi *et al*, 2023) or treatment of pregnancy-related gingivitis (Chambilla; Vásquez, 2007). Oral hard tissues could also benefit, such as through expectant treatment of caries, by stimulating dentin biomineralization by circumpulpal odontoblasts (Londoño-Lemos; Bustamante, 2019) or post-extraction dental socket bone repair by

stimulating stem cells involved in bone neoformation in healthy patients (Martel; Buitrón; Bernardo, 2019).

Figure 2 summarizes the evidence regarding taspine and its influence on different cell types and the extracellular matrix in tissue regeneration.

Figure 2: State-of-the-art of taspine and its potential in tissue regeneration.



Source: Research data.

DISCUSSION

Taspine can be considered a potent and biocompatible bioactive compound, although scientific evidence supporting its use in human or veterinary medicine has progressed at a slow pace in recent decades (Lopes *et al*, 2013). One hypothesis to explain the lack of preclinical biological studies with taspine from the natural sap of dragon's blood lies in international principles of vegan and cruelty-free products, as well as in current legislation that limits the testing of cosmetic products on animals to verify safety and efficacy (Brasil, 2025).

The predominance of connective tissue as key to the modulatory process of taspine and dragon's blood is intriguing, given the stimulation of fibroblasts and their

collagenesis, and of endothelial cells and their angiogenesis, and the collateral effect on keratinocytes. The explanation for this could lie in the common mesenchymal derivation of connective tissues, as well as in the classic reciprocal ecto-mesenchymal heterocellular interactions of embryonic tissues that persist in adult tissues such as epithelial-connective tissues (Santosh; Jones, 2014), even though the cell signaling pathways and gene expression in response to the bioactive substance remain poorly understood.

Dragon's blood and taspine are used in commercial products linked to the pharmaceutical industry, with more foreign products being associated with them than specifically Brazilian ones (Lopes *et al*, 2013). Within a new scenario of translational research and innovation in healthcare for the national biopharmaceutical segment (Gadelha; Vargas; Alves, 2019), the bioactive compound taspine could be innovative in therapies for the recovery of injured tissues. Its permeability offers promising therapeutic possibilities for tissue engineering proposals, either directly or implanted with biomaterials using carrier scaffolds (Joyce *et al*, 2021) or in microcapsules (Uchida, 2023) aiming for slow release and longer lasting effects (Joyce *et al*, 2021; Uchida, 2023).

Despite taspine being derived from the dragon's blood of *Croton lechleri* in South America (Londoño-Lemos; Bustamante, 2019), it is worth noting that this does not necessarily imply sustainability. Some authors argue for its accessibility and cost-effectiveness in production, as it is a natural product (Namjuyan *et al*, 2015). However, considering its primary Amazonian origin, environmental awareness is necessary when using products from traceable sources, aiming for conservation and not irrational extraction (Lopes *et al*, 2013) and the depletion of this renewable resource due to overexploitation (Martel; Buitrón; Bernardo, 2019).

Furthermore, studies are needed to improve the purification of taspine isolated from the raw material and to evaluate quality and control aspects, as well as to investigate the correct administration of clinical doses of *Croton lechleri* or the bioactive taspine, to ensure appropriate and responsible use (Peres *et al*, 2023).

CONCLUSION

The regenerative potential of taspine aligns with the positive modulation of fibroblasts, keratinocytes, collagen fibers, and blood capillaries of the extracellular matrix, with its biotechnological prospecting being more limited to the cutaneous bed.

Although traditional use is widespread and initial preclinical and clinical studies are promising, further research is needed to optimize formulations, determine ideal dosages, and deepen the understanding of their complex molecular mechanisms, especially for application in different types of body injuries and in broader populations.

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