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New Therapeutic Perspective Based on *Anacardium humile* in the Treatment of Skin Wound Infected by *Staphylococcus aureus*

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

This is a literature review with the objective of presenting scientific evidence about the therapeutic importance of the use of *Anacardium humile* for the treatment of infected skin wounds. Retrospective and analytical study carried out from 1999 to 2021, in the Bireme, UpToDate, Pubmed and Scielo databases. The association of the descriptors "Phytotherapy" was used; "Cerrado and Pantanal Plants"; "Wounds contaminated by bacteria"; "elastic fibers". Of the 248 articles analyzed, 36 were included in the review because they met the inclusion criteria. Among the results, it was evidenced that the conventional treatments, although effective (the gold standard being Sulfadiazine 1% silver), present toxicity to human keratinocytes and fibroblasts, with this, it is concluded that further research will be necessary to prove the effectiveness of new treatment options or association of herbal medicines with treatment.

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1. INTRODUCTION

The main cause of delays and aggravations in wound healing is contamination by microorganisms, burdening care in the public health system with longer hospital stays, increasing treatment costs by around 40% [1]. The bacterium *S. aureus* is the infectious agent most commonly isolated in tissue infections and there is a certain epidemic of infections with strains resistant to beta-lactams [2]. Medicinal plants present relevant alternatives in therapeutic treatments in healing and inflammatory processes for the rehabilitation of skin disorders [3]. The genus Anacardium belongs to the family Anacardiaceae. Its current taxonomy consists of about 10 species. Among the various existing species, those designated as cashews deserve special attention. Cajuí is a terminology used to describe species of the genus Anacardium that have chestnut and small peduncle. It is a native plant that is widely dispersed in the Cerrados, Northeast, Midwest and Southeast regions [4]. Agostini-Costa et al. [5], when describing Anacardium species, classified as cashew (chestnut + stalk) the following species: *A. amilcarinum, A. giganteum, A. humile, A. microcarpum, A. nanum* and *A. pumilum*. The species *Anacardium humile* has peduncles with phenolic compounds, vitamin C, minerals such as calcium, iron, phosphorus, considerable levels of sugars and low pH values, also demonstrating a great nutritional potential, which increases the use of this small cashew from the Cerrado by the processing industry of fruits [6].

2. MATERIALS AND METHODS

A search of scientific literature was carried out in the Bireme, UpToDate, Pubmed and Scielo databases, between 1999 and 2020, using the descriptors: “Phytotherapy”; “Cerrado and Pantanal Plants”; “Wounds contaminated by bacteria”; “elastic fibers”. A total of 248 articles were selected and these pre-selected articles were evaluated regarding the inclusion criteria: complete, current articles, in English, Portuguese or Spanish and from reliable platforms, those that did not meet the inclusion criteria were excluded. They were analyzed by titles and abstracts and articles that were repeated in the databases, that is, duplicates, totaling 36 selected articles.

3. RESULTS AND DISCUSSION

The skin is composed of distinct layers: dermis (rich in extracellular matrix proteins and elastic fibers) and epidermis (rich in continuous regenerative cells) [7]. In the skin, elastic fibers are present in the reticular portion, also known as dense unpatterned connective tissue, and fibroblasts are the main cells in this portion of the tissue, producing collagen and elastin proteins [8,9,10]. Elastic fibers are essential as they provide elasticity to the tissue, but as it matures, the tendency is for some of them to join collagen, thus making the tissue more resistant [11].

Wounds are considered a public health problem due to the increasing occurrences of people affected, causing disorders in the economic, social and psychological areas. In addition to interfering with quality of life, it also contributes to increases in public spending on health [12]. A wound is a disruption of the normal structure and function of the skin and soft tissue architecture. When classified as an acute wound, it demonstrates normal physiology, and healing is expected to progress through the expected stages of healing, while a chronic wound is defined as one that is physiologically impaired. All wounds are colonized by microbes; however, not all wounds are infected [13].

To identify an infected wound, clinical signs include local symptoms (cellulitis, lymphangitic streaks, purulence, malodour, wet gangrene, osteomyelitis) and systemic symptoms (fever, chills, nausea, hypotension, hyperglycemia, leukocytosis, mental status change) [14].

Characteristics of chronic wounds that prevent an adequate cellular response to healing stimuli include accumulation of devitalized tissue, decreased angiogenesis, hyperkeratotic tissue, exudate, and biofilm formation (ie, bacterial overgrowth on the wound surface) 2021.

Most chronic wounds are colonized by more than one bacterial species causing damage to the host [15] and have their healing phases disordered. The wound gains another regression condition, the cells suffer interruption in their proliferation, the keratinocytes cannot evolve with the normal migratory activity, because they do not respond to stimuli, as well as fibroblasts, which do not meet the growth factor TGF-β1 [16].

Wound healing occurs as a cellular response to tissue injury and involves the activation of keratinocytes, fibroblasts, endothelial cells, macrophages, and platelets. The process involves organized cell migration and recruitment of endothelial cells for angiogenesis. The many growth factors and cytokines released by these cell types coordinate and maintain wound healing.

Chronic wounds are trapped in one of the healing stages, usually the inflammatory stage, and fail to progress further, in these situations, the normal physiology of the linear pathway is transformed into the pathophysiology of a chronic cycle, without a clear wound closure outcome. The presence of necrotic tissue, foreign material, and bacteria results in the abnormal production of matrix metalloproteases, which alter the balance of inflammation and impair cytokine function.

Immediately after skin injury, small vessels within the wound constrict to provide a measure of hemostasis for 5 to 10 minutes (first phase of healing – hemostasis). Platelets aggregate in the cut vessels, trigger the clotting cascade, and release essential growth factors and cytokines that are important for the initiation and progression of healing (eg, platelet-derived growth factor, transforming growth factor beta). The resulting fibrin matrix stabilizes the wound and provides temporary support for the healing process.

The inflammatory phase is sometimes called the lag phase because wound strength does not immediately return. The inflammatory phase is usually completed within three days, except in the presence of infection or other factors associated with impaired wound healing.

In chronic wounds, the normal progression of healing is often stalled at this inflammatory stage. The presence of necrotic tissue, foreign material, and bacteria results in the abnormal production of matrix metalloproteases, which alter the balance of inflammation and impair cytokine function. Next, we have the epithelialization phase which refers to the proliferation of basal cells and migration of epithelial cells that occur at the fibrin bridge within a clot. Proliferation continues until individual cells are surrounded by cells of a similar type. Migration ceases when this layer is rejuvenated. The surface layer of the epithelium creates a barrier to bacteria and other foreign bodies. However, it is very thin, easily traumatized and has little tensile strength (ATINGER; STEINBERG; MEYR, 2010). Continuing with the fibroplasia stage, in which fibroblast proliferation, ground substance accumulation and collagen production occur [17]. To finally arrive at the maturation phase, in which key elements of the maturation stage include collagen crosslinking, collagen remodeling, wound contraction and repigmentation [18]. It is at this stage that we will have the presence of collagen fibers, so to be sure about the healing of a wound, it is necessary to quantify the elastic fibers present in it.

Topical antibiotics and antimicrobials are used as a way to prevent infection, reduce or eliminate the number of microorganisms present in open wounds [19]. Topical antibiotics must have broad-spectrum bactericidal action and low risk of tissue toxicity, without intervening in the healing process. In some cases, the use of these products within 1-3 hours after contamination is sufficient to prevent tissue infection. Alternatively antibiotics such as penicillin, ampicillin, tetracycline and cephalosporins, for example, can be added to the wash solution [20].

1% silver sulfadiazine has a broad spectrum against gram positive (*Staphylococcus aureus*) and gram negative bacteria (*Pseudomonas* spp, *Proteus* spp, *Escherichia coli*, *Enterobacter*, *Klebsiella* sp), and most fungi; are intended to penetrate the necrotic tissues performing debridement and assist in the epithelialization of wounds). It is one of the most effective agents in the treatment of thermal injuries due to the high risk of infection, the ointment remains effective for up to three days and the dressings can be kept for up to seven days [19]. In vitro studies suggest toxicity to human keratinocytes and fibroblasts, however, when it is associated with aloe vera, it can be reversed [21].

Another therapeutic measure that has been widely used in medical practice is the use of natural products, due to their numerous beneficial, safe and low-cost properties [22]. Phytotherapics can be strong coadjuvants in treatments, as well as associated with drugs already on the market, a need that meets new discoveries identified in plants, such as the Brazilian Cerrado biome, which has species with healing properties (CHAVES et al., 2016).

Among species of this biome is *Anacardium humile* that belongs to the Anacardiaceae family, of Brazilian origin, native to tropical America and

popular in South America, has a high concentration of flavonoids and phenolic compounds that are metabolites with anti-inflammatory, antioxidant and antibiotic power (GODINHO et al., 2015). The antibacterial action of the leaf can be a strong ally in the treatment of infections caused by pathogens capable of developing resistance to antibiotics and has received increasing attention with the increase in infections in skin and soft tissues by methicillin-resistant *S. aureus* (MRSA) [2].

The use in folk medicine of the species A. Humile is demonstrated in the Treaty of Medicinal Plants from Minas Gerais, Natives and Cultivated [23], a book based on interviews with more than 80 healers from Minas Gerais and a bibliographic survey of medicinal plants used in the state. Verde, Paula and Caneiro [24] carried out a survey in the city of Mossâmedes (GO) of the species widely used as medicinal plants by the local population, in which the leaves of the species *A. humile* were cited in the treatment of ovarian inflammation. In folk medicine, this species also has applications such as: cautery, in skin disorders, against diarrhea, cough and to lower the glucose content in diabetics [25].

The literature has few references to studies of biological activities with *A. humile*, being restricted to germination studies [26], genetic divergence between populations [27], insecticidal activities. Phytochemical investigations carried out by FERREIRA [28] led to the isolation of compounds from the secondary metabolism of *A. humile*. Among them are derivatives of gallic acid, catechins and flavonoids. In the same study, the author found that the methanolic extract of *A. humile* leaves was able to significantly inhibit the formation of ethanol-induced ulcerative lesions in Swiss rats, attributing this protective activity to the presence of the components found.

Antimicrobial or antibiotic substances constitute a special group of therapeutic agents, generally produced and obtained from living organisms. They are substances that, in small concentrations, must have lethal or inhibitory activity against many microbial species, and, in addition to preventing the development of resistant microorganisms, they must present absence of undesirable effects to the host and chemical stability, among other characteristics [29]. Plants produce a vast number of natural substances with antimicrobial and immunomodulatory potential in an attempt to adapt to environmental aggressions. These substances can be isoflavonoids, indoles, phytosterols, polysaccharides, sesquiterpenes, alkaloids, glucans, tannins, vitamins and minerals [30]. The knowledge about certain plant species with antimicrobial properties has been revised and expanded, due to the growing problems associated with the use of different antibiotics. In an extensive study on medicinal plants, a concrete evaluation was made on the antimicrobial activity of extracts, essential oils and substances obtained from plant species against Gram-positive, Gram-negative bacteria and fungal species [31].

4. CONCLUSION

New therapeutic options have emerged, among them *Anacardium humile* has shown satisfactory effects on healing, without adverse effects. Thus, further studies should be carried out with such techniques, as they present evidence that they can be effective in the treatment of contaminated wounds.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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