

Effectiveness of Phytotherapy on Tissue Reconstitution of Diabetic Foot: A Review

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Abstract

Introduction: In Diabetes mellitus (DM) there are several complications about the disease, among them diabetic neuropathy, popularly called diabetic foot, a type of wound that is characterized by its difficult healing.

Objective: To describe the effectiveness of herbal medicine in the tissue reconstruction of the diabetic foot, through a literature review.

Method: It deals with a review of literature as a documentary assessment and a descriptive approach to which research has been carried out on the electronic data bases Latin American and Caribbean Literature (LILACS), Scientific Electronic Library Online (SCIELO), Online Search and Analysis System of Medical Literature (MEDLINE-PUBMED), using different combinations of descriptors.

Results: 394 articles found, especially considering the inclusion and exclusion criteria pre-established for research, 20 selected articles for comparison with the literature review.

Conclusion: Different products of natural origin (plants and honey products) showed healing potential against diabetic foot ulcers, promoting contraction and reduction of ulcer size, accelerating healing and stimulating tissue reconstruction.

Keywords: *Diabetes Mellitus; Diabetic Foot; Phytotherapy; Natural Products*

Introduction

Diabetes Mellitus is a chronic non-transmissible metabolic disease of multifactorial origin characterized by the increase in glycemic levels due to the absence or inability of insulin to perform its physiological function generating several complications [1].

According to the guidelines of the Brazilian Diabetes Society, this pathology is an important and growing public health problem for all countries, whose increased prevalence is associated with several factors, such as rapid urbanization, epidemiological transition, nutritional transition and especially the growing population mass, in which two groups stand out, the elderly and sedentary population [2].

According to the American Diabetes Association, DM can be classified into the following categories: (a) Type 1 Diabetes mellitus (due to the destruction of autoimmunological cells, usually leading to insulin deficiency); (b) Type 2 diabetes mellitus (due to a progressive loss of adequate insulin secretion from beta cells often in the context of insulin resistance); (c) Gestational diabetes mellitus (diabetes diagnosed in the second or third semester of pregnancy); (d) Diabetes linked to other factors (monogenic diabetes syndromes; exocrine pancreas disease; chemical and/or pharmacological diabetes) [3].

One of the main complications due to DM is peripheral vascular disease (PVD), which, when associated with neuropathy, becomes one of the main causes of non-traumatic amputation. This situation favors the appearance of ulcers and hinders healing due to the lower supply of nutrients and oxygen in the lesion bed, besides favoring infectious processes due to the decreased effect of antibiotic therapy due to ischemia [4]. This complication causes muscle weakening and peripheral pathological and neurological changes of the feet, favoring the appearance of ulcers, which usually result from traumas that sometimes the patient does not notice [5].

In general, control of DM requires a change in lifestyle, combining a rule-made diet and regular physical activities. When these measures do not result in an effective reduction of hyperglycemia, continuous use of medications is necessary, and metformin, the first drug pick [6]. In particular, lesions resulting from diabetic neuropathy are deep ulcerations of the tissue, difficult to heal, usually associated with neurological alterations, differentiated degrees of peripheral vascular disease and osteoarticular deformities [7].

Peripheral neuropathy associated with diabetes (diabetic foot) is characterized by the involvement of sensory, motor and autonomic fibers, which promotes ulcerations and destruction of superficial and deep tissues. It is estimated that 15 to 25% of individuals with DM develop this complication [7]. Healing of these lesions and tissue reconstitution are difficult and amputation is one of the most serious consequences. In this context, phytotherapy appears as a non-pharmacological treatment that can accentuate tissue reconstitution and promote an advance in the healing process and make up a set of elements to be used in the treatment of diabetic foot.

Considering the difficulty of healing tissue lesions in patients with diabetic foot, the objective of this study was to describe the importance of phytotherapy in the healing process of diabetic foot, through a literature review.

Methodology

The work is a literature review with a documentary evaluation and descriptive approach, in which data collections were performed in electronic databases such as the Latin American and Caribbean Literature (LILACS), Scientific Electronic Library Online (SCIELO) and The Online System of Search and Analysis of Medical Literature (MEDLINE-PUBMED) considering the publications between the years 2010 to 2020. Also consulted were official documents published by the American Diabetes Association, International Diabetes Federation and Brazilian Diabetes Society.

To guide the research, the following search descriptors were used: “diabetic foot”, “Diabetes mellitus”, “natural products”, “phytotherapy” and “healing” in Portuguese and English. The Boolean operator used was the AND. The search limits adopted were based on publications available in full text and with free access to.

The following inclusion criteria were: indexed articles published in national and international journals, accessed in full text and delimitation of the year of publication between 2010 and 2020. On the other hand, the exclusion criteria took into account articles that after identification through titles and abstracts did not fit the objective of the research and those that were unavailable for download. Review articles, course completion papers, dissertations, theses and editorial notes were excluded.

Results and Discussion

The present study found during the research a total of 394 articles in the three databases analyzed. However, after the inclusion and exclusion criteria, 13 articles were selected to make up the literature review (Table 1). The database that provided the highest number of documents was PUBMED/MEDLINE (n = 196), accompanied by LILACS (n = 100) and SCIELO (n = 98). The combination of descriptors that provided the most documents in the three databases was “diabetic foot and phytotherapy”.

Author/Year	Objective	Type of study	How to use	Results obtained
Meimeti., <i>et al.</i> [8]	Investigate the efficacy of ointments, containing as an active ingredient olive oil extract in the treatment of patients with diabetic foot ulcers.	Randomized clinical trial.	Crude extract applied directly.	Complete ulcer healing in 61% of patients.
Huseini., <i>et al.</i> [9]	Investigate the healing activity of <i>T. polium</i> extract ointment in diabetic rats with diabetic foot ulcers.	Pre-clinical study in <i>in vivo</i> model.	Extract in the form of ointment.	Accelerated the wound healing process in relation to control Pharmacological.
Silva., <i>et al.</i> [10]	Follow the evolution of chronic ulcers in the lower limbs of people with diabetes, submitted to a three-month treatment with sap-based ointment of <i>C. lechleri</i> .	Experimental pilot clinical study, with quantitative approach.	Extract in the form of ointment.	Reduction of the average size of ulcers.
Astrada., <i>et al.</i> [11]	Report a treatment of diabetic foot ulcers using honey-based dressings.	Clinical case story.	Extract in natura in the form of dressing.	Stimulated wound healing and assisted in reepithelialization.
Mujica., <i>et al.</i> [12]	Evaluate the effect of propolis as an adjuvant in the healing of human diabetic foot ulcers.	Randomized placebo-controlled clinical trial.	Extract in natura in the form of spray	Improved and promoted healing.
Pengzong., <i>et al.</i> [13]	Evaluate the potential for wound healing and the possible mechanism of action of the standardized extract of <i>Boswellia serrata</i> in the face of the experimental ulcer model diabetic foot.	Pre-clinical study in <i>in vivo</i> model.	Gross extract in liquid form.	Increased the rate of wound contraction.
Najafian., <i>et al.</i> [14]	Evaluate the efficacy of Aloe vera gel in diabetic foot ulcer.	Randomized double-blind clinical trial.	Gel-shaped extract.	Reduction of ulcer surface.
Afkhamizadeh., <i>et al.</i> [15]	Investigate the effect of topical propolis administration on the healing of diabetic foot ulcers.	Randomized clinical trial.	Extract in the form of ointment.	Reduction of ulcer size.
Muhammad., <i>et al.</i> [16]	Evaluate the antibacterial and healing activities <i>in vivo</i> of an aqueous fraction of <i>Moringa oleifera</i> in a condition of diabetic foot ulcers.	Pre-clinical study in <i>in vivo</i> model.	Crude aqueous extract applied directly.	Reduced wound size, improved wound contraction and tissue regeneration.
Romero-Cerecero., <i>et al.</i> [17]	Evaluate the efficacy and tolerability of a phytopharmaceutical of <i>A. pichinchensis</i> extract administered patients with diabetic foot ulcers.	Randomized double-blind pilot clinical study	Crude aqueous extract applied directly.	Improved the healing process
Iabichella., <i>et al.</i> [18]	Report the successful result of <i>A. indica</i> extracts in infection and healing of diabetic foot ulcers with exposure bone, without prior use of surgical procedure.	Clinical case story.	Crude aqueous extract applied directly.	Decreased infection and accelerated wound healing.
Edmondson., <i>et al.</i> [19]	Evaluate the healing and antimicrobial potential of <i>Melaleuca alternata</i> oil in acute and chronic diabetic foot wounds.	Experimental pilot clinical study.	Essential oil with direct application.	Reduction of wound size and skin reconstitution.
Carvalho., <i>et al.</i> [20]	Test healing and debridement effects and papain solutions at 2%, 4%, 6% and 10% on diabetic foot injuries.	Experimental clinical study.	Extract in natura in the form of dressing.	Stimulation and promotion of healing and tissue debridement.

Table 1: Compilation of articles on the efficacy of phytotherapy in tissue reconstitution of diabetic foot published between 2010 - 2020. Source: Authors (2020).

According to the International Diabetes Federation [21], most patients with DM have a neuropathy or circulatory problem installed, which increases the chance of developing an ulcer. In general, ulcerations associated with neuropathy constitute the so-called diabetic foot, which is characterized by a set of traumas, deformities of anatomical structures and polyneuropathy [22].

The severity of diabetic foot ulcers can be classified according to the University of Texas scale. According to this scale, the clinical information provided allows a subdivision in degrees ranging from 0 - 3, related to the depth of the lesion, presence or absence of microbial infections and ischemia [23].

In general, the degree of classification of the ulcer, according to the scale, determines the decision about the treatment to be applied [5]. For Duarte and Gonçalves [24], the treatment of diabetic foot is based on some general basic principles such as: (a) metabolic control, (b) ulcer cleansing and healing-inducing pharmacological treatment and (c) orthopedic surgical interventions to correct hyperpressure over the ulcerated area.

A viable alternative to aid in the healing process of diabetic foot ulcers is the use of topical agents under the lesions, however, their efficacy decreases in long-term treatments and may develop, in addition to adverse effects, and bacterial resistance, in the case of infected ulcers [24]. In this context, the use of natural products in the form of essential extracts and/or oil, becomes a viable alternative in the healing process and with minimal side effects.

In this literature review it was possible to observe the healing potential of several plant species, whose extracts and/or essential oil were tested against diabetic foot ulcers, both in pre-clinical trials *in vivo* and in clinical trials.

Preclinical trials in *in vivo* models tested the efficacy of crude extracts of different plant species, in the form of ointment and liquid, applied directly on the wound, and an increase in wound contraction was observed, promoting the reduction and acceleration of the healing process in relation to pharmacological control [9,13,16].

Astrada., *et al.* [11], showed through a case report that the use of dressings based on fresh honey extract stimulated wound healing and aided in the reepithelialization of diabetic foot ulcers. The report by Iabichaella., *et al.* [18], showed that the use of crude extracts of *A. indica*, applied directly on the diabetic foot ulcer with bone exposure, caused the reduction of infection and accelerated wound healing.

An experimental pilot clinical study conducted by Silva., *et al.* [10], followed the evolution of chronic ulcers in the lower limbs of people with diabetes, submitted to the use of ointment based on extract *C. lechleri*, and observed the reduction of the average size of ulcers. The pilot clinical study conducted by Edmondson., *et al.* [19] evaluated the healing potential of *M. alternifolia* essential oil and observed a reduction in wound size and effective skin reconstitution. Romero-Cerecero., *et al.* [17], conducted a randomized double-blind pilot clinical study using the crude extract of *A. pichinchensis* and observed an improvement in the healing process in those patients who used the extract applied topically on the wound.

Several randomized clinical studies have shown the efficacy of plant extracts in the process of tissue reconstitution of diabetic foot ulcers. Meimeti., *et al.* [8] showed that the use of olive oil extract in the treatment of patients with diabetic foot ulcers promoted complete ulcer healing in 61% of the patients who participated in the study. Mujica., *et al.* [12], when evaluating the effect of crude propolis extract, in the form of spray, as an adjunct in the healing of diabetic foot ulcers, they observed an improvement in ulcer and an acceleration in

the healing process. Najafian, *et al.* [14], tested Aloe vera extract in the form of gel, through a randomized double-blind clinical trial, and observed reduction of ulcer surface. In the randomized clinical trial conducted by Afkhamizadeh, *et al.* [15], the effect of propolis extract on the healing of diabetic foot ulcers was investigated, and a reduction in ulcer size was observed in patients treated with ointments based on propolis extract. Carvalho, *et al.* [20], tested the healing and debridement effects of papain solutions at different concentrations, and observed that in natura extracts stimulated and promoted tissue healing and debridement in all concentrations tested.

Over the centuries, products of plant origin, due to their bioactive molecules, have been the basis for the treatment of various diseases, whose empirical knowledge, after generation and generation, was essential for the discovery of molecules with therapeutic properties. In this sense, Brazil, through its Ministry of Health, has encouraged the insertion of complementary care and care practices, through the implementation of the National Policy of Medicinal and Herbal Plants (PNPMF) [25] and the National Policy of Integrative and Complementary Practices (PNPIC) [26], which aim to stimulate access to complementary practices and medicinal plants.

In this context, the healing action of plant extracts is presented and discussed in the literature; and particularly for diabetic foot ulcers, the reports, although few, present promising results in relation to the development of drugs with healing action in diabetic foot ulcers based on natural products.

Conclusion

Different products of natural origin (plants and melifery products) showed healing potential against diabetic foot ulcers promoting contraction and reduction of wound size, accelerating healing and stimulating tissue reconstitution, when applied directly to the ulcer in the form of liquid crude extract, essential oil or ointment prepared with the crude extract.

The healing potential of natural products in the face of different chronic wounds, including diabetic foot ulcers, are presented in the literature through results obtained from pre-clinical and clinical trials, and these promising results are in relation to the development of medicines with healing action in diabetic foot ulcers based on natural products.

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