

Use of phytotherapy in treating diabetic foot in older adults: an integrative review

Uso da fitoterapia no tratamento do pé diabético em pessoas idosas: revisão integrativa

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ABSTRACT

Objective: to identify the scientific evidence on herbal medicines used in treating diabetic foot in older adults. **Methods:** an integrative review conducted in the Medical Literature Analysis and Retrieval System, SCOPUS, EMBASE, Web of Science and Latin American and Caribbean Health Sciences Literature databases. The Rayyan platform was used as a supporting tool for archiving, organizing and selecting articles. **Results:** the search resulted in 158 articles. After identifying, selecting, evaluating eligibility, systematization and performing a full reading of the articles, the final sample consisted of 10 articles. We identified herbal medicines derived from *Calendula officinalis*, *Ageratina pichinchensis*, *Phellodendron chinense*, *Curcumin phytosome*, *Capsicum spp.*, *Rehmannia Glutinosa* and *Astragalus membranaceus*. **Conclusion:** investigations of herbal compounds derived from four plants used in treating diabetic foot in older adults predominated. **Considerations to practice:** supported by legislation, nurses can guide users interested in using phytotherapy as an accessible solution with proven efficacy. **Descriptors:** Nursing; Diabetes Mellitus; Health of the Elderly; Diabetic Foot; Phytotherapy.

RESUMO

Objetivo: identificar as evidências científicas sobre fitoterápicos utilizados no tratamento de pé diabético em pessoas idosas. **Métodos:** revisão integrativa, realizada nas bases de dados *Medical Literature Analysis and Retrieval System*, SCOPUS, EMBASE, *Web of Science* e *Latin American and Caribbean Health Sciences Literature*. Utilizou-se a plataforma Rayyan, como ferramenta auxiliar para arquivamento, organização e seleção dos artigos. **Resultados:** a busca resultou em 158 artigos. Após a estratégia de identificação, seleção, avaliação da elegibilidade, sistematização e leitura na íntegra, a amostra final foi de 10 artigos. Identificou-se fitoterápicos derivados de *Calendula officinalis*, *Ageratina pichinchensis*, *Phellodendron chinense*, *Curcumin phytosome*, *Capsicum spp.*, *Rehmannia Glutinosa* e *Astragalus membranaceus*. **Conclusão:** predominou a investigação de compostos fitoterápicos derivados de quatro plantas utilizados no tratamento do pé diabético em pessoas idosas. **Considerações para a prática:** amparados pela legislação, os enfermeiros podem orientar usuários interessados em utilizar fitoterapia, como solução acessível e de eficácia comprovada. **Descritores:** Enfermagem; Diabetes Mellitus; Saúde do Idoso; Pé Diabético; Fitoterapia.

Introduction

Diabetes Mellitus (DM) is characterized by an increase in blood glucose levels resulting from the absence or deficiency in insulin hormone production, or even by resistance to the action of the insulin produced⁽¹⁻²⁾. Its prevalence and complications increase with age, especially for those aged 65 years or older. Following the current prevalence rates, it is estimated that 783.2 million people in the world will live with DM in the year 2045⁽³⁾. Furthermore, between 19% and 34% of diabetic patients suffer from foot ulcers throughout their lives. The annual incidence rate is 2%, and the recurrence rate after healing is 40% within one year, and 65% within three years⁽⁴⁾.

Considering old age as one of the main risk factors for developing diabetic foot ulcers (DFU), therapy should consider that older adults have a delay in the healing process and in the repair of lesions, a decrease in the inflammatory response that reduces the collagen metabolism, in addition to a decrease in epithelialization and angiogenesis⁽⁵⁾. In this context, the importance of the multidisciplinary team is highlighted, especially the role of nurses who have legal support and technical-scientific knowledge for treating wounds⁽⁶⁾.

In the context of chronic wounds, herbal medicines are a possible solution to abandon treatment early, a strategy to approach popular knowledge, and to provide the development of self-care and the autonomy of the individual within their treatment process⁽⁷⁻⁸⁾. A literature review which analyzed 27 studies that addressed the effectiveness of using medicinal plants in treating wounds showed their great relevance in the healing process⁽⁷⁾. There are countless studies which attest to the effectiveness of plants known for their healing, anti-inflammatory, analgesic or antimicrobial properties. However, for a herbal medicine to be considered therapeutic, it must undergo a rigorous evaluation process which proves its beneficial effect, usually conducted in experimental design research⁽⁹⁾.

Thus, in view of the gap pointed out in the li-

terature about the insufficient specific knowledge on the part of professionals about the subject, even with the use of such natural resources since the dawn of humanity, it is essential to know the scientific principles of the use of plants and their herbal derivatives by health professionals, especially nurses, as well as the exchange between scientific knowledge and popular traditions considering the frequent use of plants as an alternative therapeutic effect, their potential benefits and their access to the population⁽⁷⁻¹⁰⁾.

In this context, an in-depth investigation of the effectiveness of the main herbal medicines which are the object of experimental research in treating diabetic foot and its associated conditions is necessary, with the aim of supporting professionals in the therapeutic decision-making process regarding medicinal alternatives which have proven effectiveness. Thus, the objective of this study was to identify the scientific evidence on herbal medicines used in treating diabetic foot in older adults.

Methods

This is an integrative literature review, a method which aims to seek similarities and differences between the articles raised in the reference documents in order to gather information on a given topic⁽¹¹⁾. The following steps were followed: elaboration of the guiding question, search or sampling in the literature, data collection, critical analysis of the included studies, discussion of the results and presentation of the integrative review⁽¹²⁾. The search, evaluation, selection, characterization and analysis procedures of the articles were performed by two trained researchers in pairs, who met for consensus in cases of disagreement during the month of January 2022.

The guiding question of the study was formulated in the first stage using the PICO strategy - Population, Intervention, Comparison, Outcomes (results), being Population (older adults with diabetic foot), Intervention (use of phytotherapy), Comparison (none) and Outcomes (Diabetic foot treatment). This strate-

gy helps in analyzing and organizing clinical practice problems, and facilitated creating the following guiding question: Which herbal medicines are used to treat diabetic foot in older adults?

In the second stage, only original intervention studies were included with the primary objective of investigating the effectiveness of using phytotherapy in treating diabetic foot in a population aged 60 years or older, without restriction regarding the publication year or language. Review studies, letters, conference abstracts, book chapters, case reports and study protocols were excluded, as well as studies in the animal testing phase.

The search in the third stage was conducted in the following databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via Pubmed, Scopus, Embase, Web of Science and Latin American and Caribbean Literature in Health Sciences (LILACS) via the Library Virtual Health (VHL). The controlled descriptors in English of “phytotherapy” and “diabetic foot”, from the health terminology of Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), along with the Boolean AND, were adopted for each database. Filters were not applied in the scientific bases in order to expand the search due to the scarcity of studies. The Rayyan platform developed by the Qatar Computing Research Institute (QCRI) was used as a support tool for archiving, organizing and selecting articles⁽¹²⁾.

Next, the level of evidence was verified in the fourth step to assist in choosing the best possible evidence according to the research design: Level 1: evidence resulting from the meta-analysis of multiple randomized controlled clinical studies; Level 2: evidence obtained from individual studies with an experimental design; Level 3: evidence from quasi-experimental studies; Level 4: evidence from descriptive studies (non-experimental) or with a qualitative approach; Level 5: evidence from case reports or experience; Level 6: Evidence based on expert opinion⁽¹¹⁾.

A thorough reading of the articles was subse-

quently performed, the publications were filed and a descriptive analysis of the selected information was carried out. Data collection took place by extracting information regarding the study characteristics (authors, publication year, study type, sample) and the intervention characteristics (medicinal plant description, effect duration and outcome). Data were documented in a spreadsheet prepared by the authors.

The results were presented and the data discussed descriptively, focusing on the medicinal plant used, its characteristics, application form, usage time and evaluation of effectiveness.

Results

The search in the databases resulted in identifying 158 articles. After identifying, selecting, evaluating eligibility, systematizing and reading the articles in full, the final research sample consisted of 10 articles which deal with the use of different herbal presentations in treating diabetic foot and which included older adults in their samples. The strategy for eligibility and inclusion of studies is outlined in Figure 1.

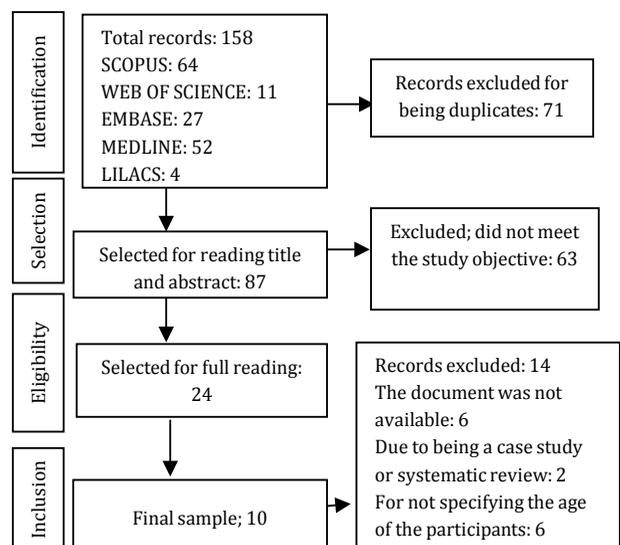


Figure 1 – Flowchart of the article selection process adapted from the recommendation of Preferred Reporting Items for Systematic reviews and Meta-Analyses⁽¹³⁾. Fortaleza, CE, Brazil, 2022

According to the publication language, nine (90%) studies were available in English and one (10%) in Portuguese, 10 (100%) were intervention studies, with 40% being quasi-experimental studies and 60% randomized controlled trials. Chinese studies predominated regarding nationality with three (30%), followed by two Brazilian (20%), one German (10%), one Mexican (10%), one Pakistani (10%), one Italian (10%) and one Iranian (10%).

The training area of the authors of the studies was verified. Thus, studies whose authors were mostly physicians or linked to medical schools predominated with six (60%), followed by two biologists (20%), one pharmacist (10%), and one physiotherapist (10%). None of the studies had authors linked to nursing schools or who were mentioned as nurses.

Regarding the critical evidence level analysis of

the studies, 40% of the studies are of level of evidence III, as they did not present the randomization description of the studies. However, it is noteworthy that 60% of the studies presented level of evidence II.

The herbal medicines were derived from plants *Calendula officinalis*, *Ageratina pichinchensis*, *Phellodendron chinense*, *Curcumin phytosome*, *Capsicum spp.*, *Rehmannia Glutinosa* and *Astragalus membranaceus*, as well as *Tangzu Yuyang Ointment* (TYO), a compound derived from nine herbal medicines.

The studied medicinal plants, author, year and country of origin, as well as the compounds or active principles used, average age of the participants or age group of the study sample, application method proposed by the researchers and the main findings of the authors of the studies are presented in Figure 2.

Author/ Year/ Country	Medicinal plant	Study type and level of evidence	Application method	Age of participants (years)	Main findings
A ⁽¹⁴⁾ Forst et al, (2002) Germany	<i>Capsicum spp.</i>	Quasi- experimental study Level of evidence III	Cream (0.05%), for 8 weeks	64.8; ± 2.4	The study found a beneficial effect of topical capsaicin treatment on symptomatic diabetic neuropathy without affecting sensory nerve fiber function or neurovascular control over the eight-week period.
B ⁽¹⁵⁾ Appendino et al., (2011) Italy	<i>Curcuma longa</i>	Quasi- experimental study Level of evidence III	Two tablets (1g Meriva/day), for four weeks / Lecithinized formulation	58.1; ± 3.5	Meriva showed potential in managing diabetic microangiopathy. Of note, a fibrinolytic enhancement was observed in some patients, particularly those with a mild increase in fibrinogen levels and altered fibrinolysis.
C ⁽¹⁶⁾ Li et al, (2011) China	<i>Coptis chinensish</i> , <i>Ligusticum chuanxiong</i> , <i>Atractylodes lancea</i> , <i>Panax notoginseng</i> , <i>Angelica sinensis</i> , <i>Arnebia euchroma</i> , <i>Phellodendron chinense</i> , <i>Rheum officinale</i> , <i>Borneolum syntheticum</i> , <i>Demonorops draco</i> , <i>Gypsum fibrosum praeeparatum</i>	Randomized Clinical Trial Level of evidence II	Ointment	60; ± 12 (38 – 80)	The study proved the potential, efficacy and safety of the compound Tangzu Yuyang Ointment for the treatment, suggesting that it accelerates DFU healing.
D ⁽¹⁷⁾ Ko et al., (2014) China	<i>Rehmannia Glutinosa</i> , <i>Astragalus membranaceus</i>	Randomized Clinical Trial Level of evidence II	Granulated powder distributed in sachets, 2 sachets (5g/day)	74.0; ± 12.0	The study demonstrated the clinical benefits of NF3 accompanied by molecular changes in the systemic circulation that may explain its healing and anti-inflammatory action. The positive effects of NF3 on sensory neuropathy require further evaluation.

(the Figure 1 continue in the next page...)

Author/ Year/ Country	Medicinal plant	Study type and level of evidence	Application method	Age of participants (years)	Main findings
E ⁽¹⁸⁾ Romero- Cerecero et al., (2014) Mexico	<i>Ageratina pichinchensis</i>	Quasi- experimental study Level of evidence III	Extract	63; ± 12.33	<i>A. pichinchensis</i> extract demonstrated the ability to enhance the healing process in patients with DFU. However, no statistically significant differences were observed when compared with the results obtained in patients who received silver sulfadiazine.
F ⁽¹⁹⁾ Buzzi, Freitas e Winter (2016) Brazil	<i>Calendula officinalis</i>	Quasi- experimental study Level of evidence III	Hydroglycolic extract	62 (44–82)	The use of <i>C. officinalis</i> hydroglycolic extract was associated with a high percentage (78%) of healed DFU.
G ⁽²⁰⁾ Carvalho et al., (2016) Brazil	<i>Calendula officinalis</i>	Randomized Clinical Trial Level of evidence II	Calendula EFA associated with LLLT	Patients aged between 40 and 70 years were included	It is concluded that low-intensity laser therapy alone or in association with <i>Calendula officinalis</i> oil is effective in relieving pain due to its anti-inflammatory action, and in reducing the total area of ulcers by stimulating neovascularization and accelerating cell proliferation.
H ⁽²¹⁾ Musharraf, Ahmad and Zernab (2017) Pakistan	<i>Capsicum spp., Pistacia terebinthus</i>	Randomized Clinical Trial Level of evidence II	Capcidol® Cream Lotion/Oil vs Turpentine oil; topical use	Included patients aged between 18 and 70 years	The study demonstrated that turpentine oil has similar efficacy to capsaicin cream in treating diabetic neuropathic pain. Treatment with capsaicin and turpentine oil is safe and free from side effects associated with systemic therapies.
I ⁽²²⁾ Liu et al., (2020) China	<i>Phellodendron Chinese Forsythia suspensa Lonicera japonica Taraxacum mongolicum Scolopendra</i>	Randomized Clinical Trial Level of evidence II	Topical use compound	63.7; ± 9.53 (38 – 80)	In the external treatment of DFU, the compound can promote ulcer healing and increase the serum concentration of growth factors, being safe and reliable in external clinical use.
J ⁽²³⁾ Mokhtari, Razzaghi and Momen- Heravi (2021) Iran	<i>Curcuma longa</i>	Randomized Clinical Trial Level of evidence II	SinaCurcumin® Capsules Nano-Micellar Soft gel (80mg Curcumin), oral use	57.4 ± 11.7, in the control group	The study demonstrated that ingestion of nano-curcumin in patients with DFU resulted in a significant improvement in fasting blood glucose, plasma insulin levels, HOMA-IR, total cholesterol, low-intensity lipoprotein, and glutathione levels, among others, but did not affect ulcer size, HbA1c, other lipid profiles, inflammation markers or oxidative stress.

DFU: Diabetic foot ulcers; EFA: Essential fatty acids; HbA1c: Glycated hemoglobin; HOMA-IR: Index to assess insulin resistance; LLLT: Low Level Laser Therapy; NF3: Traditional Chinese Medicine composed of two herbs

Figure 2 – Characterization of selected studies regarding title, publication year, journal, methodology and objectives. Fortaleza, CE, Brazil, 2022

Discussion

Traditional Chinese Medicine herbs stood out when analyzing the state of the art for using phytotherapy in treating diabetic foot in older adults in the literature; this treatment is based on principles such as the theory of *yin-yang* and *Qi* (vital energy), and is used in treating hundreds of diseases based on treatment techniques perfected over more than 4,000 years in this culture⁽²⁴⁾.

It is important to highlight that Brazilian flora offers great prospects for research and for producing medicines and health supplies, in addition to representing one of the richest sources of material with bioactive potential on the planet and the potential of medicinal plants such as *Embaíba*, *Copaíba* and *Capeba*⁽²⁵⁻²⁶⁾. However, there is little research or registration of products which have explored the potential of Brazilian medicinal plants, especially with regard to diabetic foot treatment.

The investigation of compounds derived from four plants predominated in the sample, such as *Calendula officinalis*, which is traditionally used to promote the healing process of wounds and ulcers, and also investigated for its analgesic, antidiabetic and anti-inflammatory properties⁽²⁷⁾. Its applicability in DFU treatment was evaluated by a clinical trial on the effectiveness of calendula oil alone and associated with low-intensity laser therapy. However, they did not find statistically relevant differences between the use of herbal oil alone and the referred therapy⁽²⁰⁾.

A compound applied in the form of topical spray had the use of 4% *Calendula officinalis* hydroglycolic extract. It was associated with a high percentage (78%) of healed DFU. Wound pain ratings were significantly reduced at the end of the treatment period⁽¹⁹⁾. Thus, it is possible to perceive the need for longitudinal research and with a larger sample to deepen the action mechanisms of the herbal medicine.

Another plant with medicinal properties is *Phellodendron chinense*. When analyzing the clinical application of a fluid composed of *cortex phellodendri*

in DFU treatment, it was found that it can promote ulcer healing and increase the serum concentration of growth factors⁽²²⁾. Furthermore, among the medicinal properties of *Phellodendron chinense*, it is justifiable to evaluate the efficacy and safety of using Tangzu Yuyang Ointment (TYO) for treatment. Thus, TYO therapy associated with standard treatment for chronic diabetic foot ulcers is more effective than the isolated use of standard therapy for DFU, with few side effects⁽²⁸⁾.

The third most cited medicinal plant genus was *Capsicum* spp. The topical application of a cream based on the herbal medicine in small fiber neuropathy and neurovascular control was analyzed in an investigation into the efficacy of capsaicin, and it was concluded that topical use of capsaicin in symptomatic diabetic neuropathy had a beneficial effect without adversely affecting sensory nerves⁽¹⁴⁾. From another perspective, the effectiveness of the topical use of turpentine oil compared to capsaicin cream in diabetic neuropathic pain relief was investigated, leading to the conclusion that turpentine oil is effective in controlling diabetic neuropathic pain in a similar way to capsaicin cream⁽²¹⁾.

When evaluating the action of curcumin on diabetic microangiopathy, the authors concluded that Meriva (curcumin lecithinized formulation) has potential in treating diabetic microangiopathy⁽¹⁵⁾. A study with another design investigated the effects of supplementation with nanocurcumin capsules in the wound on healing parameters and metabolic control in patients with DFU, presenting significant results in the improvement of fasting plasma glucose, plasma insulin levels after ingesting nanocurcumin, without affecting the ulcer size or impacting HbA1c (glycated hemoglobin)⁽²³⁾.

Ageratin is yet another genus which has also been shown to be effective in treating DFU. The efficacy and tolerability of a phytopharmaceutical developed with a standardized extract (5% cream) of *Ageratina pichinchensis* was evaluated through topical application in patients with DFU, in which all patients who completed the study achieved complete healing of their ulcers⁽¹⁸⁾.

Rehmanniae Radix is the washed tuberous root of *Rehmannia glutinosa*, and was also cited in this review. When investigating the effects of a herbal compound based on *Astragali Radix* and *Radix Rehmanniae* on DFU healing and the molecular mechanisms associated with this process, a reduction in the ulcer area of 3.55% per day was observed in the group that received the treatment with the herbal medicine, and 1.52% in the placebo group⁽¹⁷⁾.

It is noteworthy that the prolonged inflammatory state caused by DM increases oxidative stress due to an overproduction of several reactive oxygen species and reactive nitrogen species, which have a notable cytotoxic and pro-degradative potential in the ulcer area, leading to impairment in the healing process. Thus, the action of these herbal compounds acts as a potent anti-inflammatory and antioxidant action that stimulates healthy neovascularization⁽²⁹⁾.

In addition, it is important to emphasize that the healing process of wounds in older adults has some factors which can make treatment difficult, such as cognitive dysfunction, physiological changes related to the integumentary system, in addition to mishaps in adherence to treatment due to functional disability, lack of glycemic control and malnutrition⁽³⁰⁾. Empowering older adults with diabetic foot ulcers and their family members and/or caregivers regarding care is extremely relevant; however, the presence of nurses in this process is essential, as older adults commonly have a family tradition regarding the use of herbal medicines and the use combination of plants and drugs can cause a drug interaction which can interfere with the treatment effectiveness⁽³¹⁾. Therefore, professional care centered on older adults with longitudinality, adapted, preventive and permanent education becomes essential, given the need for systematization regarding education, screening, risk reduction and treatment of these ulcers⁽³⁰⁾.

The number of studies conducted by nurses is insufficient, which signals the need for further research to explore this gap. In addition, there were few studies that evaluated the effectiveness of drugs directly

with the older adult population and that considered the physiological particularities inherent in the aging process, as well as more studies which addressed the effectiveness of herbal medicines that are native to Brazil, a country that paradoxically has one of the greatest bioactive potentials on the planet.

Study limitations

A limitation of the study which stands out was the difficulty of finding studies that specified the age of their participants and that were in the application phase in humans. In addition, due to the study type, it was not possible to assess the bias of the studies in this review, requiring further studies with a higher level of evidence to guide treatments with herbal medicines in diabetic foot ulcers. It is imperative that there are investigations directly developed by nurses addressing the perspective of professional care along with the use of various integrative therapies.

Contributions to practice

The majority of studies in this review are in the medical field. However, care for wounds and ulcers, as well as healthcare from the perspective of promoting, preventing, recovering and rehabilitating health in different diseases and conditions, as in the case of care for patients with diabetic foot syndrome, is intrinsic to Nursing practice. In addition, as health educators and under the protection of legislation, nurses can advise on the use of phytotherapy, which is an accessible and effective method.

Conclusion

The herbal medicines used in treating diabetic foot in older adults were identified in the literature. Studies that analyzed the effectiveness in humans of herbal compounds from Traditional Chinese Medicine plants, such as *Calendula officinalis*, *Ageratina pichinchensis*, *Phellodendron chinense*, *Curcumin phytosome*,

Capsicum spp., *Rehmannia Glutinosa* and *Astragalus membranaceus*, in addition to the compound Tangzu Yuyang Ointment. There was a level of evidence II in most studies. Furthermore, it was common to investigate drugs composed of one more plants or different pharmacological presentations of the same plant, such as extracts, creams, oils and food supplements.

Authors' contribution

Conception and design or data analysis and interpretation; manuscript writing or relevant critical review of intellectual content; responsibility for all aspects of the text in guaranteeing the accuracy and integrity of any part of the manuscript: Pires JM, Lopes GF, Sousa CR, Oliveira FGL, Souza RLP.

Conception and design or data analysis and interpretation; manuscript writing or relevant critical review of intellectual content; final approval of the version to be published; responsibility for all aspects of the text in ensuring the accuracy and integrity of any part of the manuscript: Coutinho JFV, Marques MB.

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