

STUDY PROTOCOL

Topical Effects of Aloe Vera in Healing Diabetic Foot Ulcers: A Protocol of Systematic Review

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ABSTRACT

Introduction: Wound care is a very important part of managing diabetic foot ulcers. The importance of choosing the right topical therapy for managing diabetic foot ulcers aims to help speed up the wound healing process. Aloe vera is one of the traditional natural ingredients that is often used in wound care and can maintain a moist atmosphere in wound care. So it is necessary to have a systematic review to provide comprehensive evidence regarding the topical effects of aloe vera in increasing wound healing in diabetic foot ulcers. This study aims to determine the topical effect of aloe vera in healing diabetic foot ulcers. **Methods:** This research is a systematic completion that will use six databases (CINAHL, Academic, PubMed, ProQuest, ScienceDirect, SpringerLink, and google scholar) to search for randomized controlled trial and Quasi-Experimental articles randomly in 2007-2022. The Systematic Review protocol used follows PRISMA as a guide in preparing insights and The Joanna Briggs Institute (JBI) Critical Appraisal Tools to assess research quality. This study will determine the effect of topical aloe vera on wound healing in diabetic foot ulcers. **Discussion:** The results of this study can be useful for knowing the topical effects of aloe vera for wound healing in diabetic foot ulcers. **Trial Registration:** This protocol has been registered on the protocol registration site for systematic review namely PROSPERO with registration number CRD42022318695.

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INTRODUCTION

Diabetes is a threat in Indonesia, where the epidemic is still likely to increase. Indonesia according to the International Diabetes Federation (IDF) in 2019 is the only Southeast Asian country that is included in the list of 10 countries with the highest diabetes sufferers (1). Indonesia is ranked seventh in the world with around 10.7 million diabetics (2). Basic Health Research reported a significant increase in the prevalence of diabetes at the age of ≥ 15 years, from 6.9% in 2013 to 8.5% (20.4 million) in 2018.

One of the long-term microvascular complications caused by diabetes mellitus is diabetic foot ulcers. Diabetic foot ulcers are caused by a process of peripheral neuropathy, peripheral arterial disease, or a combination of both. Diabetic foot ulcers are wounds on all layers of the skin, necrosis or gangrene which usually occurs on 1-2 soles of the feet, due to peripheral neuropathy or peripheral arterial disease in people with

diabetes mellitus (3).

The standard of care (SOC) for the treatment of diabetic foot ulcers currently consists of five principles, namely offloading, debridement, infection management, selection of wound dressings and revascularization when indicated (4). The combination of offloading, debridement, and infection control is used in the selection of wound dressings (5-7). The above method is a treatment method that is currently developing, namely modern wound dressing dressing with the principle of moisture balance, which is stated in some literature to be more effective for the wound healing process when compared to conventional wound care methods (8-10).

As modern wound care develops, there are also some drawbacks and drawbacks that patients and service providers cannot avoid. One of them is the need for more funds to be able to access the types of modern wound dressings that exist. Thus the use of traditional topical drugs has been widely developed and researched as an alternative in accelerating the healing process in a cost-effective manner (11). One of the traditional natural ingredients that is often used in the treatment of wounds, especially diabetic foot ulcers, is aloe vera.

Aloe vera is the most biologically active plant species. The components contained in aloe vera are mostly water, reaching 99-99.5%. There are more than 75 other potentially active components of aloe vera such as vitamins, minerals, saccharides, amino acids, anti quinones, enzymes, lignin, saponins and acids containing salts (12).

Aloe vera is known to accelerate the healing process of various wounds. Aloe vera components such as aloin, amino acids, chrysophanic acid, glucomannan, protease, vitamins C and E are known to accelerate the wound healing process in each of its phases (13). Some recent literature concludes that aloe vera supports inflammation, increases wound contraction and epithelialization, reduces necrotic tissue, and improves alignment and organization of regenerating scar tissue (14, 15). The high water content in aloe vera can keep the wound moist and increase the migration of epithelial cells. Aloe vera can block the action of catecholamines, thereby helping to increase the epithelialization process. Aloe vera can also increase collagenization, stimulate the production of macrophage cytokines (13).

Topical use of aloe vera as an alternative therapy in the treatment of diabetic foot ulcers is a form of problem solving in improving patient wound healing. Topical use of aloe vera is based on various studies that can scientifically prove the effects of topical aloe vera on diabetic foot ulcers. Therefore, researchers are interested in conducting a systematic review with the title "topical effect of aloe vera in improving wound healing of diabetic foot ulcers". The formulation of this research question is based on the PICO mnemonic. It has been used most frequently in systematic reviews and is centered on four main concepts: Population or Problem, Intervention or Exposure, Comparison and Outcome Measures. Based on these principles, where comparative aspects do not apply, studies should cover three main aspects in the review, namely patients with diabetic foot ulcers (Population or Problem), wound care using topical aloe vera (Intervention or Exposure) and wound healing (Outcome Measures), which will then guide this study to formulate its main research question "What is the effect of topical aloe vera in wound healing of diabetic foot ulcers?". In principle, systematic review research begins with making a research protocol, therefore this systematic review protocol is important. This protocol enables the authors to conduct a systematic review effectively and precisely, provides better team communication, and simplifies producing the report. Furthermore, the authors in this study protocol can describe the literature, rationales, and methods in more detail. The general aim of this systematic review was to analyze the effect of topical aloe vera on wound healing of diabetic foot ulcers and to provide evidence for or against the hypothesis that topical aloe vera has an effect on enhancing healing in diabetic foot ulcer patients.

METHODS

Study design

This systematic review followed PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) as a guide developing research protocols in a systematic way. This review has been registered on the systematic review protocol registration site, namely PROSPERO with registration number CDR42022318695. The PRISMA checklist which contains 27 items will be used as a guide in preparing the review (16). The PRISMA flow diagram will be used to determine the selection of systematic review studies (17). The overall goal of PRISMA is to help ensure clarity and transparency in systematic literature review reporting (18).

Search strategy

Researchers will use an electronic database consisting of CINAHL, Academic, Pubmed, Proquest, Sciencedirect, Springerlink and Google Scholar as a source of information to identify relevant studies. Each search will be limited to randomized controlled trial and quasi-experimental design published in English and Indonesian during 2007-2022. The article search will use keywords that will be matched with MeSH (Medical Subject Heading). Boolean operators (AND, OR, NOT) will also be used to expand and define search results so as to make it easier to select articles to include in a review (19). The search strategy is explained in English: (diabetic foot ulcer OR diabetic foot OR foot ulcer OR chronic wound OR chronic ulcer) AND (aloe OR aloe vera OR aloe barbadensis OR aloe barbadensis mill) AND (healing OR wound healing OR re-epithelization OR regeneration) and in Indonesian: (ulkus kaki diabetik ATAU kaki diabetik ATAU ulkus kaki ATAU luka kronik ATAU ulkus kronik) DAN (aloe ATAU aloe vera ATAU aloe barbadensis ATAU aloe barbadensis mill) DAN (penyembuhan ATAU penyembuhan luka ATAU re-epitelisasi ATAU regenerasi).

Eligibility criteria

The limitations of the review questions were determined precisely through the application or inclusion and exclusion criteria by applying the PICOS format (Table 1) (20). Studies were considered for inclusion in the review, if the following criteria were met: randomized controlled trials (RCTs) and quasi experimental trial in English and Indonesian between 2007-2022; the population is diabetic foot ulcer patients who receive wound care intervention; describe topical effect of aloe vera. Exclusion criteria were: randomized controlled trials (RCTs) and quasi experimental trials published other than 2007-2022; cross sectional studies, case studies and qualitative studies; study focus that is irrelevant to the research objective.

Screening and data extraction

Researchers will screen titles and abstracts based on eligibility criteria to identify studies that have the

Table 1: PICOS Framework

PICOS Framework	Inclusion Criteria	ExclusionCriteria
Population	Diabetic foot ulcer patients	Not a diabetic foot ulcer patient
Intervention	A study examining wound care interventions with topical aloe vera in diabetic foot ulcer patients	A studies examining interventions other than topical aloe vera or other irrelevant interventions.
Comparison	None	None
Outcomes	A study that explains the effect of topical aloe vera on wound healing	A study that explains other effect of topical aloe vera on wound healing
Study design and publication type	Randomized control trial, quasy experiment	Cross-SectionalStudy, Case Study dan Qualitative Study
Publication years	2007-2022	Other than 2007-2022
Language	English and Indonesian	Other Languages

potential to be included in review. In particular, the title and abstract will be included, if the study reports relevant information on the effects of topical aloe vera in diabetic foot ulcer patients. Researchers will take a copy of the full text of the article to be assessed at a later stage. Studies that seem relevant but were excluded at this stage will be listed in the “Characteristics of excluded studies” table, where the reasons for exclusion will be noted. Researchers will verify the final list of included studies. To provide an overview of the decisions taken during the data collection phase, a PRISMA flow diagram of the study selection procedure will be created. Researchers will extract and manage data for each included study. The data to be collected in each article consists of study demographics (author, year of publication, study objectives, location, study design, hypotheses), respondent characteristics (age, gender, and ulcer grade), intervention characteristics (type of aloe vera topical preparation, duration of intervention, control/intervention conditions, measurement time points and study result) and result in the form of wound healing measurement and conclusions (17, 21, 22). The PRISMA flow diagram presented in figure 1.

Quality assessment

The risk of bias from this study will be assessed by the Joanna Briggs Institute (JBI) critical assessment tool in analyzing the quality of the methodology in each study. The JBI use is randomized controlled trials tools containing 13 assessment criteria and quasi experimental tools containing 8 assessment criteria (23). Each criteria is rated ‘yes’, ‘no’, ‘unclear’, or ‘not applicable’, and each measure is scored ‘yes’ and is awarded one point. The assessment score for each article is based on JBI with a minimum cut off value of 50%. Studies with a score below 50% will not be included in the review process to avoid bias in the result and discussion (21, 24, 25).

Data analysis

The analytical method that will be used in this systematic literature review is descriptive analysis using content

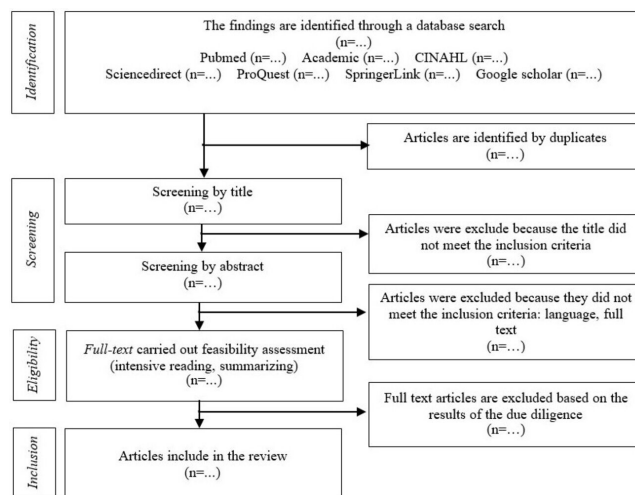


Figure 1: The PRISMA flow diagram

analysis techniques that present the findings of the literature in a narrative manner. In writing this systematic literature review, no additional analytical methods will be added. The researchers will only summarize the result in the articles and analyze them according to the content. The result of the measurements to be analyzed are the topical effect of aloe vera in increasing the healing of diabetic foot ulcers. The stages of analysis that will be used in this systematic literature review are a comprehensive process consisting of four interrelated stage, namely reading the contents of the article in dept from all research result, making by line the fundings of the study, compiling sentences or findings that are marked based on similarity in meaning to in the themes presented in descriptive writing, and interpreting analytical themes then poured in the results of the review. This systematic review will be synthesized using the narrative method by grouping similar extracted data according to the measurement result to answer the research objectives. The data is then made into a summary of the journal, including the name of researcher, year of publication, title of article, research objective, research locations, research samples, methods, intervention, and a summary of the result or funding. Summary of research articles will be entered into a table sorted by year of publication of the article and alphabetically according to the format (21, 26). The data extraction results presented in table II.

DISCUSSION

Aloe vera can be considered as an economical, readily available, safe, and effective topical agent in the treatment of wounds. Aloe vera, which has an acidic pH, is considered to be the main factor responsible for accelerating wound healing. Aloe vera can also accelerate wound healing by increasing the activity of glycolytic enzymes and providing sufficient energy for cell recovery (27, 28).

One of the features of the proposed study is to use a

Table II: Data extraction result

No	Author (Year)	Title	Country	Research Design	Sample characteristics	Research instrument	Intervention	Control	Result
		reproducible and transparent approach to carry out a systematic review of the literature. We explicitly specified the types of studies, participants, treatments and outcomes to be included in this protocol, as well as data sources, search strategies, data extraction techniques (including quality evaluations), and data aggregation procedures (29). By disseminating study procedures, we strengthen the clarity of strategy while reducing the danger of bias, particularly the selective reporting of results (30). Second, we will only focus on the topical effects of aloe vera on diabetic foot ulcer wound healing. These results will provide high-level information to inform, support, and adjust decisions regarding wound care actions. This literature study can be used as a reference for nurses in developing standard operating procedures and clinical guidelines in providing wound care in patients with diabetic foot ulcers. A study reported that the application of Aloe vera on diabetic ulcers gave some benefits and offer a better wound healing (31).							
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